Systematic Review: Natural History of Histologically-proven Alcohol Related Liver Disease

Systematic review: liver and non-liver mortality in hospitalized patients with histologically-proven alcohol related liver disease

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Abstract

Background: Studies into the natural history of alcohol related liver disease (ArLD) to date have lacked long-term follow-up, large numbers of participants, or both. We performed a systematic review to summarise studies that describe the natural history of histologically-proven ARLD.

Methods: PubMed and Medline were searched for relevant studies according to pre-specified criteria. Data were extracted to describe the prevalence of ArLD, histological progression of disease and mortality. Single proportion meta-analysis was used to combine data from studies regarding rates of progression or mortality.

Results: Thirty-seven studies were included, reporting data from 7,528 participants. Amongst cohorts of hazardous drinkers, on average 15% had normal histological appearances, 27% had hepatic steatosis, 24% had steatohepatitis and 26% had cirrhosis. Annualised progression of pre-cirrhotic disease to cirrhosis were 1% (0-8%) in patients with normal histology, 3% (2-4%) in hepatic steatosis, 10% (6-17%) in steatohepatitis and 8% (3-19%) in fibrosis. Annualised mortality was 6% (4-7%) in patients with steatosis and 8% (5-13%) in cirrhosis. In patients with steatohepatitis on biopsy a marked difference was seen between inpatient cohorts (annual mortality 15%, 8-26%) and mixed cohorts of inpatients and outpatients (annual mortality 5%, 2-10%). Only in steatosis did non-liver related mortality exceed liver-specific causes of mortality (5% per year vs. 1% per year).

Conclusions: These data confirm the observation that alcohol related hepatic steatohepatitis requiring admission to hospital is the most dangerous sub-type of ArLD. Alcohol-related steatosis is not a benign condition as it is associated with significant risk of mortality. There were insufficient data to reliably describe the effect of drinking behaviour on progression of disease or on mortality, or to describe outcomes beyond crude mortality rates, highlighting the need for high-quality natural history studies.

Lay summary

Knowledge of the natural history of a disease allows clinicians and patients to understand the risks that are associated with a medical condition. In this study we systematically gathered all the published data regarding the natural history of alcohol related liver disease in people who had a liver biopsy to define the prevalence of the disease, the annual risk of progression to cirrhosis and the annual risks of death at each stage of the disease.

Alcohol related liver disease (ArLD) is common throughout the world (1). ArLD is a leading cause of liver related morbidity and mortality (2) and a frequent cause of death amongst people of working age (3). Hazardous drinking – consumption of alcohol at levels that are likely to cause harm – is prevalent globally (4). This is a prerequisite for the development of ArLD, which covers a spectrum of disease from steatosis, steatohepatitis to cirrhosis. Earlier stages of disease are considered reversible with abstinence from alcohol. (5). Liver-specific morbidity and mortality is only considered to occur with more advanced disease.

Good quality natural history studies exist for most liver diseases but only relatively few describe the prevalence or progression of histologically-defined ArLD. Population-based studies such as the Dionysius study in northern Italy (6) are useful but have necessarily relied largely on ultrasonography to define liver disease. Mixed results have been observed on the association between histological parameters and progression of alcoholic liver disease. Hepatic steatosis, considered the earliest stage of ArLD can progress to cirrhosis (7, 8) and other studies have confirmed the high risk of death in alcohol-related cirrhosis (9). The relationship between alcohol intake and prevalence, progression and death is not straightforward in these studies, where other aetiological factors may play a significant role (10). However, several prospective population studies have shown that self-reported alcohol intake is a good predictor of the future risk of alcohol induced diseases (11).

An accurate understanding of the natural history of ArLD is necessary for prognostication and communication with patients. This is not well defined at present. Using the PICOS tool (participants, interventions, comparisons, outcomes and study design), this study sought to use published observational data to describe the prevalence, progression and mortality in people with biopsy-proven ArLD.

Methods

A systematic review was undertaken by searching PubMed (1948 – present) and MedLine (1946 – present) using the MESH terms 'alcoholic liver disease', 'prevalence', 'natural history' and 'epidemiology'. The search strategy is described in full in the supplementary material. This review was registered with the PROSPERO database. Searches were performed on the 31st May 2018 and limited to English language and human studies. Full papers and abstracts were included. Risk of bias in included studies was based on the Newcastle-Ottawa tool (12).

Data Analysis

Data were analysed for three principle outcomes: 1. prevalence of histological sub-types of liver disease, 2. progression of pre-cirrhotic liver disease to cirrhosis and 3. mortality (overall, liver-specific mortality and non-liver mortality). Pre-specified sub-analyses were planned for abstinent/non-abstinent patients. For the purposes of analysis four histological stages of ArLD were considered: steatosis, steatohepatitis, fibrosis not amounting to cirrhosis and cirrhosis. Linear progression through these stages was assumed. Progression or mortality rates were calculated by dividing the total number of events by the median follow-up duration in years to get the annual number of events. Overall prevalence, progression rates and annualised mortality rates were calculated with single-proportion meta-analysis, using 'meta' in R (13). Random effects meta-analysis was used to generate an overall proportion with 95% confidence intervals. Sensitivity analyses were done to distinguish between the histological diagnosis of steatohepatitis and the acute clinical syndrome of alcoholic hepatitis. To attempt to distinguish between these entities in the included studies we examined data regarding the prevalence of jaundice, the average serum bilirubin concentration and the proportion of patients who had been admitted to hospital acutely at the time of liver biopsy. Of these variables, only the proportion of patients who were admitted to hospital was reported frequently enough to be used in sensitivity analysis.

The sub-categories of non-liver-related and liver-related mortality were not analysed in the sensitivity analysis as too few data were available.

This systematic review is reported according to the MOOSE statement (14) (**supplementary material**).

Results

The literature searches yielded a total of 46,043 results, of which 49 were reviewed in more detail, yielding 25 studies suitable for inclusion. Searching reference lists and citing literature yielded a further 12 studies (**figure 1**). In total, 37 studies including 7,528 participants were included. The characteristics of patients in each study are shown in **table 1**. The assessed risk of bias was fairly uniform across the studies (**supplementary table 1**), only a few studies explicitly included consecutive patients, raising the risk of selection bias, and few had independent assessment of biopsies by pathologists blinded to the clinical scenario. Some studies relied on registry data without access to original patient records.

Prevalence of ArLD amongst hazardous drinkers

Fifteen studies including a total of 3,474 patients reported on histological liver disease in hazardous drinkers (15–18) (19) (20–26) (27–29) (**table 2**). The prevalence of each histological sub-type of ArLD was 15% (95%CI 7-18%) for normal histological appearances, 27% (21-38%) for steatosis, 24% (12-28%) for steatohepatitis, 27% (19-46%) for fibrosis not amounting to cirrhosis and 26% (19-36%) for cirrhosis (**table 2**). When studies that included consecutive patients were compared to those that did not, more normal histology was found (19% vs. 9%), and fewer cases of steatohepatitis (15% vs 26%) or steatohepatitis with cirrhosis (10% vs. 13%).

The indication for liver biopsy varied significantly between studies, no study included consecutive hazardous drinkers without additional caveats, for example presentation to

hospital, or raised AST. Only one study included patients from primary care settings (28), all others were based on hospitalised patients. There was variation with regard to the histological scoring system used to grade fibrosis with some using the METAVIR system (30) or recent papers using the system proposed by Kleiner et al for grading of non-alcoholic fatty liver disease (NAFLD) (31). Most studies reported histological features individually such that overlapping disease was not recognized, however the study from Chedid et al reported 'pure' findings from sicker patients, this may account for the outlying values from this study compared to others. The variation in reporting may account for the wide inter-quartile ranges. There were insufficient data reported in the included studies to consider alcohol intake for each histological category.

Progression of disease

Nine studies including 918 participants described histological progression of disease using paired liver biopsies (5, 7, 8, 32–37). None of these studies used protocol biopsies at planned intervals, instead biopsies taken in the course of clinical care or autopsy results were used to describe histological progression. The median time between biopsies was 7 years. The overall annual progression from pre-cirrhotic disease to cirrhosis was 4% (95% CI 2 – 11%). The rate of progression to cirrhosis varied between histological subtypes: annualised progression rates to cirrhosis were 1% (95%CI 0 - 8%) for patients with normal appearances on biopsy at baseline, 3% (95%CI 2 – 4%) for steatosis, 10% (95%CI 6 - 17%) for steatohepatitis and 8% (95%CI 3 – 19%) for any grade of pre-cirrhotic fibrosis (**figure 2, supplementary table 2**). The single report of disease progression to cirrhosis from normal renders this finding highly inaccurate.

There were insufficient data about alcohol use in included studies to analyse the effect of abstinence or alcohol on rates of progression. Only one study included information about progression rates in abstinent versus non-abstinent patients, where progression from steatohepatitis to cirrhosis was 18% in abstinent patients over 1.7 years, versus 23% in non-

abstinent patients (5). Very few of the included studies reported on regression of liver disease; those that did observed low rates of regression of steatohepatitis to 'minimal histological changes' (12% per year)(5), but normalisation of liver histology was not seen (32, 37)(**supplementary table 3**).

Mortality in ArLD

Three sub-types of mortality were considered: overall mortality, non-liver related mortality and liver-specific mortality. Twenty-three studies described mortality outcomes (7, 9, 15, 17, 18, 22, 25, 33, 35, 38–49). In the eight studies (including 1091 participants) that reported mortality in alcohol related steatosis (7, 9, 18, 25, 43, 45, 46, 49), overall annual mortality was 6.0% (95%CI 4.0 – 7.0%), annual non-liver mortality was 4.0% (95%CI 3.0 – 6.0%) and annual liver-related mortality was 1.0% (95%CI 1.0 - 2.0%) (**figure 3, supplementary table 4**).

In the seven studies (including 732 participants) that reported mortality in alcohol related steatohepatitis (9, 18, 25, 35, 42, 44, 45), overall annual mortality was 11% (95%CI 6.0 – 19.0%) annual non-liver mortality was 4.0% (95%CI 2.0 – 9.0%) and annual liver-related mortality was 7.0% (95%CI 3.0 – 14.0%) (**figure 4, supplementary table 4).**

In the seven studies (including 930 participants) that reported mortality in alcohol related cirrhosis (9, 18, 22, 25, 38, 41, 48) overall annual mortality was 8.0% (95%CI 5 – 13%) annual non-liver mortality was 2.0% (95%CI 1.0 – 4.0%) and annual liver-related mortality was 6.0% (95%CI 3.0 – 10.0%) (**figure 5, supplementary table 4**).

Information regarding mortality in abstinent or non-abstinent patients was only available for three studies, each regarding alcohol related cirrhosis. These studies reported on a total of 519 participants with information about alcohol intake (of whom 187 were abstinent during follow-up and 332 continued to consume alcohol). Median annual mortality was 4.7% (IQR 4 -7%) in abstinent patients, and 8.0% (IQR 6.2 – 11.2%) in non-abstinent patients. This difference was not statistically significant (Mann Whitney test p=0.229).

Sensitivity analyses

A series of sensitivity analyses was performed to attempt to distinguish between the acute clinical syndrome of alcoholic hepatitis and the histological diagnosis of steatohepatitis by comparing studies that reported on cohorts of patients who had been admitted to hospital, to those studies that included both inpatients and outpatients. In studies that only included hospitalised patients, the incidence of steatohepatitis was greater (20% (12-33%) vs. 16 (8-29%), progression from steatohepatitis to cirrhosis was more common (14% of individuals each year (7 – 26%) vs. 8% (3 – 19%)) and overall mortality was greater (15% per year (8%-26%) vs. 5% per year (2%-10%), compared to studies that described cohorts of both inpatients and outpatients (**supplementary figures 1-4**).

Discussion

This is the first systematic review that summarises existing knowledge on the natural history of ArLD. The data show that histological evidence of ArLD is common amongst hazardous drinkers, usually pre-cirrhotic although approximately one quarter of individuals will have cirrhosis. Our results confirm that steatohepatitis is a distinct phenotype within the spectrum of ArLD characterised by higher rates of progression to cirrhosis and worse mortality. However this is only the case amongst hospitalised patients with steatohepatitis – mixed cohorts of inpatients and outpatients with steatohepatitis showed a similar mortality to patients with steatosis alone. Mortality in hospitalised patients with steatohepatitis is higher than that associated with cirrhosis highlighting the influence of marked inflammatory response in these patients and its serious consequences. The causes of mortality differed across the spectrum of ArLD: In alcohol-related hepatic steatosis mortality was mainly driven by extra-hepatic causes, whilst mortality was predominantly liver-related in steatohepatitis and cirrhosis.

In addition, these data uphold previous observations that alcohol-related hepatic steatosis is not a benign condition with annual mortality rates of approximately 6% each year. This is driven predominantly by non-liver causes, as liver-related deaths were only noted to occur at a rate of 1% each year. It cannot be proven from these data but it is likely that deaths in this group are largely a consequence of the known extra-hepatic risks of hazardous alcohol use such as malignancies or cardiovascular disease. The relevance of the presence of hepatic steatosis on these events is not clear although recent data suggest an independent effect of hepatic steatosis on cardiovascular dysfunction (50).

The annual mortality rate for patients with steatohepatitis reported here – 14.8% - is notable for being lower than in studies of patients with a clinical diagnosis of alcoholic hepatitis where the average six-month mortality rate is approximately 38% (51). The contrast is probably due to differences in patient characteristics between epidemiological studies of relatively well patients, as reported here, and acutely unwell patients admitted to hospital with severe alcoholic hepatitis. It is notable that the paper by Chedid et al (18) which included many patients with acute alcoholic hepatitis is an outlier amongst the other studies included in this review, with higher mortality rates. Histological steatohepatitis may be present without the clinical syndrome of alcoholic hepatitis (52) and this distinction is important as the short-term outlook in acute disease is poor. The sensitivity analyses performed here confirm this with greater progression to cirrhosis and greater overall mortality in cohort of patients who were admitted to hospital at the time of the index biopsy. It is a difficulty with the source data used in this study that this issue cannot be more precisely addressed.

This study has limitations, principally related to the limitations of the data we were analysing. There were too few studies to allow for robust meta-regression (53) and consequently the calculation of annual progression and mortality rates relied on average values. This relies on the assumption of uniform distribution of mortality over the course of follow-up, which may not be accurate. However sufficient data to allow for more accurate time-dependent

mortality risk was not available. The data used for meta-analysis were very heterogenous and this is reflected in the large I^2 values (for example, 75% in assessment of progression to cirrhosis from fibrotic disease and 83% for assessment of mortality in steatohepatitis). This is probably a consequence of multiple factors: the assorted methods of assessment and reporting of histological disease among studies, the drinking behaviour of different cohorts after baseline liver biopsy, and the type of cohort recruited in the first instance. This heterogeneity is a limitation of this study, and measures to allow this to be addressed should be considered in future studies.

Studies without histology were not included as we wanted to focus on biopsy-proven disease. This will necessarily have excluded studies where patients are not biopsied and introduced a bias. That said, histological outcomes can be calibrated with clinical diagnoses, for example in the study by Dam-Larsen et al (43) 22% of patients with pure alcohol related steatosis were diagnosed with cirrhosis on clinical grounds over the 13 years of follow-up, a rate of 1.7%/year, similar to the 2%/year derived from studies based on histology. In addition differences in the indication for biopsy varied between studies – some were part of routine practice but others were for research purposes. Most commonly, studies reported biopsies that had been performed during routine clinical practice where indications will have varied among clinicians, and among centres. Very few of the included studies reported in protocol-driven biopsies in consecutive patients.

Relying on histology is not without its drawbacks. One potential source of bias is regression to the mean. There is probably some variation in histological severity purely due to sampling variation. Patients who already have cirrhosis are much less likely to have a repeat biopsy. Therefore those who are followed up and have a repeat biopsy are selected by having pre-cirrhotic liver disease. Due to sampling variation, some of these will have cirrhosis on repeat biopsy purely as a result of regressing to the mean rather than true progressive disease. There is of course a similar issue with patients who appear to have regression in fibrosis. This is a problem in clinical practice as well as research cohorts. Unfortunately there is no way to reliably estimate the effect that this might have on the results.

Our search strategy did not search explicitly exclude patients admitted to hospital with acute alcoholic hepatitis, but the inclusion criteria at least one year of follow-up meant that several large series of patients with alcoholic hepatitis were excluded. There was not enough information included to separate patients with the acute clinical syndrome of alcoholic hepatitis, from those with the histological entity of steatohepatitis. This is an important distinction and should be explored in much greater detail in future studies.

Past, present and future alcohol use is critical to understanding prognosis in ArLD (38, 47). However, this was not reported in sufficient detail in most of the included studies to be included in analyses. Other missing data were common in the included studies, for example biochemical values and anthropometric data were commonly not reported, precluding meta-regression analysis. A lack of baseline data meant that prediction of progression or death in terms of baseline characteristics could not be evaluated.

Another issue is the lack of a single accepted histological scoring system for ArLD. Scoring systems specific to ArLD been proposed, for example from an international group in 1981 (54) and more recently a system for grading alcoholic steatohepatitis (55), and in some of the included studies scoring systems developed for other liver diseases were c-opted for use in ArLD for example the METAVIR score or the Kleiner-Brunt classification. More commonly, authors used a process that was specific to their study. The lack of a single scoring system may not significantly impact on gross findings such as cirrhosis, but more subtle signs such as early fibrosis may not be comparable between studies. This is a major limitation not just of this systematic review but of the field in general – steps to encourage the widespread adoption of a clinically relevant scoring system for the whole spectrum of ArLD would be of great value.

This systematic review used robust literature searching to summarize existing information on the natural history of ArLD. This allowed us to address fundamental aspects of ArLD such as prevalence, progression and prognosis. However, important questions remain that could not be addressed due to limitations of existing data. Cause of death had to be

addressed in broad terms ‘non-liver related’ and ‘liver related’, whereas more specific causes of death would be informative. Similarly, progression to cirrhosis was based on histology but biopsy is rarely used in clinical practice. Clinically relevant events such as development of ascites, variceal bleeding or hepatocellular carcinoma would be of more value to clinicians and patients.

Predictive and prognostic factors for progression in ArLD need to be addressed in large systematic prospective populations. Understanding the progression of disease and likelihood of death is important for effective communication with our patients, for public health purposes and for design of research studies. This systematic review gives useful information, but the major value of this project may be to highlight current shortcomings in the field that can be addressed in future studies.

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Figure 1: literature search flow chart

Figure 2: histological progression of non-cirrhotic alcohol-related liver disease to cirrhosis **A** annual progression from normal to cirrhosis **B** annual progression from steatosis to cirrhosis **C** annual progression from fibrosis (falling short of cirrhosis) to cirrhosis **D** annual progression from steatohepatitis (without cirrhosis) to cirrhosis

Figure 3: mortality in alcohol-related steatosis **A** annual overall mortality **B** annual non-liver related mortality **C** annual liver-related mortality

Figure 4: mortality in alcohol-related steatohepatitis **A** annual overall mortality **B** annual non-liver related mortality **C** annual liver-related mortality

Figure 5: mortality in alcohol-related cirrhosis **A** annual overall mortality **B** annual non-liver related mortality **C** annual liver-related mortality