Alcoholic Hepatitis

Incidence, Mortality, Prognostic Scoring and Causes of Death

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Papers on which this thesis is based

I. Sandahl TD, Jepsen P, Thomsen KL, Vilstrup H.
Incidence and mortality of alcoholic hepatitis in Denmark 1999-2008: a nationwide population based cohort study.
J Hepatol. 2011;54:760-4 .

II. Sandahl TD, Jepsen P, Ott P, Vilstrup H.
Validation of prognostic scores for clinical use in patients with alcoholic hepatitis.
Scand J Gastroenterol. 2011;46:1127-32

III. Ørntoft N, Sandahl TD, Jepsen P, Vilstrup H.
Causes of death in patients with alcoholic hepatitis in Denmark
Submitted

INTRODUCTION

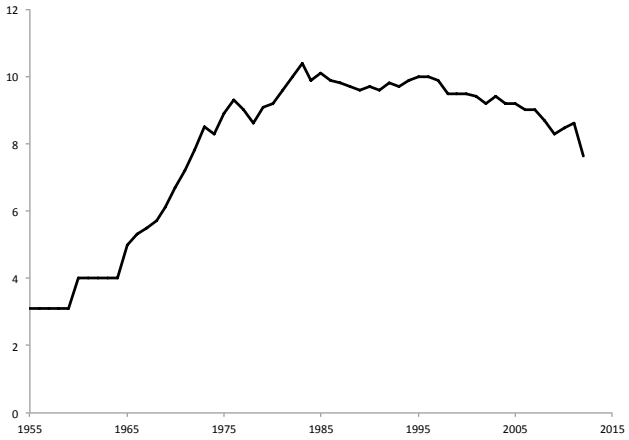
Alcoholic hepatitis (AH) is an acute life- and health-threatening disease. However, accurate and representative epidemiological data on its incidence and prognosis are not available. This is a hindrance in clinical and mechanistic studies because the necessary power analyses can not be safely conducted. Furthermore, the lack of data also has impact on the clinical care and the patient counselling. Therefore, and in analogy with our department's longstanding tradition for register-based epidemiology, we found that we could use data from the Danish nationwide databases to follow a cohort of close to 2000 patients with AH diagnosed over a 10-year period. This gave us a unique opportunity not only to answer our questions on incidence and mortality, but also to gather further information on the clinical course of the disease. This cohort forms the backbone of the present thesis. The aims of the work were: 1) To provide population based data on the incidence and short-, and long-term mortality of AH. 2) To evaluate and compare the prognostic models currently used in AH. 3) To describe the short- and long-term causes of death in AH.

BACKGROUND

Alcohol consumption in Europe and Denmark

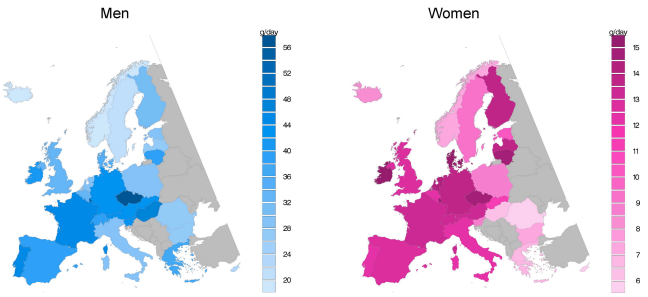
The prerequisite for developing AH is heavy drinking. According to the WHO, the world's highest alcohol consumption levels are found in the developed world, including Europe.

Figure 1. Amount of pure alcohol sold in Denmark 1955-2012 (litres per capita)



The estimated worldwide consumption of pure alcohol was 6.13 litres per person aged 15 years or older in 2005.(1) Denmark has, like most European countries, seen a sharp rise in per capita alcohol consumption after the end of World War II. The amount of pure alcohol sold in Denmark stabilised in the 1980s at approximately 10 litres of pure alcohol per person (all ages) per year, and has declined modestly since (Figure 1).(2) Compared to other countries in Europe, Denmark is positioned in the middle- to high-end regarding per capita average alcohol consumption (Figure 2).(3) It has been estimated that approximately 20% of the Danish population are heavy drinkers, defined as consuming >14/21 drinks/week (women/men).(4)

Figure 2. Daily average alcohol consumption (in g/day) per capita in European countries around year 2000.(3)



Burden of Alcoholic Liver Disease

The total costs of alcohol consumption to the EU in 2003 has been estimated to a staggering €125 billion, equivalent to 1.3% of the gross domestic product.(5) Direct cost of alcohol-related health problems accounted for €66 billion of this, while lost productivity, unemployment, and premature mortality accounted for a further €59 billion.(5) In comparison, the reported contribution to the EU goods account balance was around 9 billion Euros.(5) The general effect of alcohol consumption on health is detrimental, with an estimated 3.8% of all global deaths and 4.6% of global disability-adjusted life-years attributable to alcohol.(6) Moreover, the association between alcoholic liver disease (ALD) and alcohol consumption has been well documented, and per capita alcohol consumption is correlated with liver cirrhosis mortality rates across countries.(7, 8) The WHO now recognises alcohol as the third leading risk factor for poor health in Europe, responsible for approximately 200,000 deaths each year(1).

Alcoholic Fatty Liver disease and Cirrhosis

Chronic alcohol use may cause several types of liver injury. Alcoholic liver disease (ALD) is often perceived as a continuum of increasingly severe liver lesions. Steatosis (also called alcoholic fatty liver disease) is the mildest and most frequent form. The mechanism by which ethanol causes steatosis and liver injury is complex, but one contributor is that alcohol-dependent changes in liver metabolism lead to accumulation of triglycerides within the hepatocytes.(9, 10) This condition is regarded as benign and usually resolves following abstinence from alcohol, but steatosis also predisposes patients to liver injury, fibrosis, and cirrhosis if they continue drinking.(11)

Cirrhosis of the liver is the end-stage of most liver diseases regardless of the underlying aetiology. The risk of alcoholic cirrhosis seems to increase proportionally with the alcohol intake, but some studies indicate that customary consumption of more than 30 g of alcohol per day is required.(12, 13) As the liver is continually damaged by alcohol, fibrosis develops as a wound-healing response. With progressing fibrosis, the architecture of the liver is gradually destroyed, and the patognomic histological picture with regenerative nodules surrounded by severe fibrosis occurs.(14) The architectural changes lead metabolic impairments and portal hypertension, and the resulting ascites, oesophageal varices, variceal bleeding, hepatic encephalopathy, malnutrition and infections dominate clinical hepatology.(15) After the diagnosis of alcoholic cirrhosis has been established, the 5-year survival is dismal at only 37.5%, and alcohol consumption continues to worsen the prognosis even after cirrhosis has developed.(16, 17)

Alcoholic Hepatitis

The clinical syndrome of jaundice and liver failure in alcohol abusers is typically called “acute alcoholic hepatitis” or “alcoholic hepatitis”, which is the most serious manifestation of the alcoholic liver disease spectrum. The clinical presentation of AH is heterogeneous and ranges from mild to severe and AH is often associated with the systemic inflammatory response syndrome (SIRS) and moderate fever, with or without infection. It is important to distinguish between the clinical and pathological definitions of AH. Up to thirty-five percent of all heavy drinkers will have signs of alcoholic steatohepatitis in liver biopsies even though they may never develop the clinical syndrome.(18, 19) The short-term prognosis of severe AH is known from clinical trials(20, 21). However, population-based studies on time trends in its incidence and long-term prognosis are not available. This was the focus of Study I.

The diagnosis of alcoholic hepatitis

There are no standards or international consensus on the diagnostic criteria for AH. The combination of normal to mildly elevated aminotransferasesl, a total serum bilirubin level of more than 80 µmol per litre, an elevated INR, and neutrophilia in with a history of heavy alcohol use is suggestive of AH. However, several other liver diseases can cause this clinical presentation, and to differentiate AH from e.g. acute-on-chronic liver failure in terminal cirrhosis can be challenging. According to the present guidelines set forth by the European Association for the Study of the Liver (EASL), liver biopsy is not required to make the diagnosis, but the findings on a biopsy may be helpful to secure the diagnosis, especially in atypical cases.(22) The question of liver biopsy in AH remains controversial, and the debate is on-going. (23, 24) The fact that the diagnostic criteria of AH are not clear is a limitation of this thesis, since the 3 studies rely on registry based discharge diagnosis. This will be discussed below.

Treatment of alcoholic hepatitis

The most important factor for survival of patients who have alcoholic liver disease is abstinence from alcohol(16, 25). Any other treatment effort is probably futile useless abstinence is achieved, and therefore, abstinence should be the primary goal in the treatment of AH.

A large variety of drugs and therapies have been tested in AH, but unfortunately no unequivocal clear therapeutic benefit has been observed for any compound.(26-44) Corticosteroids and pentoxifylline are currently the drugs of choice for severe AH.

Prognostic Scores used in alcoholic hepatitis

The introduction of the Maddrey Discriminant Function (Maddrey DF) was a step forward for clinicians in identifying subgroups of patients with a poor prognosis and has been used in many randomised controlled trials to define “severe AH”.(45) Later, several scoring systems have been developed, including the model for end-stage liver disease (MELD) score, the Glasgow alcoholic hepatitis score (GAHS), the Lille model, and the ABIC score (Age, serum Bilirubin, INR, and serum Creatinine score) as predictors of survival in patients with AH.(20, 21, 46-49)

Table 1. Markers include in the scoring systems

Score	Bilirubin	INR/PT	Creatinin	Age	Albumin	Urea	Leukocytes	Na	Δ-Bilirubin
MELD	✔	✔	✔						
MELD+Na	✔	✔	✔					✔	
GAHS	✔	✔		✔		✔	✔		
Lille-model	✔	✔	✔	✔	✔				✔
ABIC-score	✔	✔	✔	✔					

MELD = Model of End stage Liver Disease, GAHS = Glasgow Alcoholic hepatitis Score
ABIC = Albumin-Bilirubin-INR-Creatinine

The scoring systems rely largely on the same biochemical core measurements and can all be seen as an extension of the Maddrey DF (Table 1). The scores have been developed in different clinical settings, e.g. using different diagnostic criteria and treatment strategies (Table 2). The different developmental cohorts have to be considered when applying the scores in clinical practice.

Table 2. Development cohorts of the scoring systems

Score	Published	Development cohort	Original validation cohort	Treatment	Optimal Cut-off	Biopsy verified
MELD	2000	231	+	+	21	No
GAHS	2005	241	195	No treatment	9	No
Lille-model	2007	320	118	Corticosteroids*	0.45	Yes
ABIC-score	2008	103	80	Corticosteroids*	6.71 / 9.0	Yes

+ The MELD score was developed for patients undergoing TIPS and not AH
* Corticosteroids was given to patients with a Maddrey DF above 32

The MELD score was originally developed for Transjugular Intrahepatic Portosystemic Shunt (TIPS) patients but is now widely used in liver diseases. In a retrospective report of patients with AH, a MELD score > 21 was associated with a 3-month mortality of 20%.(47)
The GAHS was developed in a cohort of patients clinically diagnosed with AH, and the diagnosis was not verified by biopsy. The patients did not receive pentoxifylline or corticosteroids.(46) Although easy to calculate, the GAHS has not been validated prospectively or in biopsy-proven AH.

The ABIC score was developed in patients with biopsy-proven AH, and patients with Maddrey DF>32 were treated with corticosteroids. ABIC scores of < 6.71, 6.71-8.99, and ≥ 9 predicted a 90-day survival of 100%, 70%, and 25% respectively. The ABIC score introduces the category of intermediate severity, but the possible benefit of this additional category remains to be shown.
The Lille Score is a dynamic model used to assess the treatment response at day 7 of steroid therapy (not to assess baseline severity of AH). It was developed in patients with biopsy-proven AH, and patients with Maddrey DF > 32 were treated with corticosteroids. The Lille score uses markers of liver function at baseline and the change in bilirubin concentrations on day 7 of corticosteroid therapy (www.lillemodel.com). In the original cohort, 6-month survival was 25% in patients with a Lille score > 0.45 vs 85% in those with a Lille score < 0.45.(20)
It has been attempted to use these prognostic models to guide treatment, and both the GAHS and the Lille model have been shown to identify patients who might benefit from corticosteroid therapy.(20, 21) Nevertheless, clinical scores should not enter clinical practice without external evaluation, and while some of the scores have been evaluated in other centres, a combined unbiased external validation of the most important scores in AH is not available.(50) In Study II we, therefore, compared the discriminative performance and external validity of the scoring systems by applying them to a patient population both temporally and geographically different from the original ones.

Clinical course of and causes of death in alcoholic hepatitis
The clinical course of AH is highly dependent on disease severity. For severe AH (Maddrey DF > 32), the short-term mortality is known from clinical trials and case series, and 1-month mortality is reported at approximately 30%.(46, 51) The short-term causes of death are known only from selected patient groups, and the long-term causes remain essentially unknown.(52, 53) In Study I, we found that when patients survive the initial phase of AH and the acute liver disease had resolved, they still have a high long-term mortality.(54) This finding suggests the development of chronic sequelae, such as cirrhosis, immune dysfunction or alcoholic cardiomyopathy known to be associated with AH and further data are needed(55-57) (58). A description of the short- and long-term causes of death in AH could help address this issue, and this was the focus of Study III.

AIMS

Study I
To describe the incidence, and short-, and long-term mortality of AH in a nationwide cohort of patients with 10 years' follow-up.
Study II
To evaluate and compare the predictive performances of the GAHS; the MELD score; the Lille model; and the ABIC score in a population-based unselected cohort of patients with AH.
Study III
1) To describe the short- and long-term causes of death in AH patients in a nationwide cohort of patients with AH followed for up to 10 years. 2) To assess the risk of progression to cirrhosis after the first episode of AH.

PATIENTS AND METHODS

Setting

We conducted a population-based cohort study of all patients with a hospital discharge diagnosis of AH in the entire country of Denmark, which has a population of 5.4 million. Alcohol overuse can have enormous social and economical consequences for the individual and is more prevalent in low socio-economic classes.(59) In countries with insurance-based or privately financed healthcare, there is a risk of underestimation of the incidence and prevalence of AH because some patients never are referred or admitted to the hospitals. All Danish citizens enjoy universal, tax-financed healthcare, enabling access to diagnostic and therapeutic procedures in public hospitals. No private hospitals diagnose or treat patients with AH.

Data Sources

Since the 1930s, The Danish government has compiled nearly 200 databases on everything from medical records to socioeconomic data. Consequently, Denmark has earned a reputation for possessing a vast collection of statistics that allows large cohort studies that are impossible in most countries. The data used in this thesis were obtained from the following existing population-based registries and databases.(60)

Danish National Registry of Patients

The Danish National Registry of Patients has recorded data on all inpatients treated in Danish non-psychiatric hospitals since 1977. It is mandatory to report to the DNRP, and the data include each patient's personal identification number, dates of admission and discharge, and diagnoses and procedures performed as recorded by the attending physician. Until 31 December 1993 diagnoses were recorded using the ICD-8 and from 1994 and onwards using ICD-10. DNRP is, among other things, used to monitor health care in Denmark and assess the Danish diagnosis-related groups (DRG). DRG is a measure of the health care costs and is used by the government for administrative purposes.

The Civil Registration System
The Danish Civil Registration System (CRS) is an administrative registry that keeps track of vital status, marital status, and residential address for all Danish citizens. Each citizen is provided a unique identification number immediately after birth. It was established in 1968 and is updated continuously. The system is very important because it serves as a unique identifier in almost all other databases in Denmark. Besides healthcare, this includes all government databases, banking, insurance, etc. We used the CRS to obtain complete follow-up data including dates of death.(61, 62)

The Clinical Laboratory Information Systems (Study II only)
The clinical laboratory information system is used at Danish hospitals as the backbone of daily clinical practice.(63) It is used to order and display laboratory tests. Virtually all tests performed at the hospital and in general practice are handled by the system, and the results are available online for all doctors in the region. Data include date and time of test, test unit, test name and code according to IUPAC (International Union for Pure and Applied Chemistry). Although most of Denmark is now included in the database, laboratory data were only available for the County of Northern Jutland and the County of Aarhus during the study period, these two areas comprising a total population of 1.1 million.(63)

The Danish Registry of Causes of Death
The Danish Registry of Causes of Death contains information on all death certificates since 1943, and is maintained by the National Board of Health.(64) The physician who is responsible for verification of death immediately reports the causes of death directly to the Registry. Data from autopsies are also recorded when available.

Study Design
In all three studies, we applied a population-based cohort study design and had up to 10 years' follow-up.

Study population & outcome

Study cohort
For Studies I, II, and III, we identified all patients in Denmark with a first-time hospital discharge diagnosis of AH (ICD-10 code K70.1) from 1999 and through 2008. Patients with a concurrent or previous diagnosis of hepatocellular carcinoma or viral hepatitis were excluded. AH was first introduced as a specific diagnose in ICD-10 in 1994. We chose to start our data collection in 1999; 5 years after the introduction of ICD-10 in order to make sure that clinicians were familiar with the new ICD-10 AH diagnosis and to avoid erroneous inclusion of prevalent cases. For the included patients, we obtained data on diagnoses of alcoholic cirrhosis (ICD-10 code K70.3) recorded before or concurrently with AH. Dates of death were ascertained from the Central Office of the Civil Registration System.

Study I (Incidence and mortality)
Study I was a descriptive study of the incidence of AH, as well as its short- and long-term mortality.

Study II (Validation of prognostic scores)
In Study II, we compared and evaluated the ability of different commonly used clinical scores to predict mortality in AH. These scores rely on standard blood test results (Table 1). Because laboratory data were not available for all of Denmark, we restricted the original cohort of patients from 5.4 million (all of Denmark) to a region of Denmark with a population of 1.1 million comprising the counties of Aarhus and Northern Jutland. We chose to evaluate the predictive properties of the models on 28-, 84- and 180-day mortality because these intervals were used in the developmental cohorts of the scores specifically designed for AH: GAHS (28- and 84- day mortality), Lille model (6-month mortality) and ABIC score (90-day mortality). This makes it possible to compare our findings with the original cohorts.

Study III (Causes of death)
We restricted the original cohort to include only patients dying due to AH in all of Denmark from 1999-2008. The primary outcome of interest was cause of death. We categorised deceased AH patients by gender, age at the time of death, and time since admission for AH. To distinguish the deaths related to an acute AH episode from the deaths occurring after recovery from AH, we chose to divide the observation period in two: Deaths occurring within the first 84-days of submission were categorised as related to the acute episode of AH, and deaths occurring after 84-days was categorised as unrelated to the acute episode of AH.

Causes of death
In Denmark, the causes of death are recorded as a series of ICD-10 diagnoses: an underlying, main mandatory disease diagnosis and up to four other conditions describing the chain of events leading to death. Consequently, the majority of the deceased AH patients have multiple contributing causes of death registered, which necessitated the establishment of a hierarchy to establish one main cause of death for each patient. Establishing a hierarchy must be done with caution because of the inherent risk that the hierarchy itself can affect the results. To accommodate this issue, we established a hierarchy and conducted a sensitivity analysis in which we changed the hierarchy of the ranks to estimate the impact of the chosen hierarchy on the results. The hierarchy is described in detail in Study III.

Progression to cirrhosis
To estimate the risk of progression to cirrhosis, we began the follow-up for acquired cirrhosis at 180 days after the AH diagnosis, and we considered all of the cirrhosis cases that were diagnosed earlier as having had undiagnosed cirrhosis at the time of AH diagnosis. The date of diagnosis of cirrhosis was the admission date of the first hospital contact that resulted in a discharge diagnosis of cirrhosis.

Continued Harmful drinking
Recurrent AH was classified as a readmission that resulted in a discharge diagnosis of AH. After the discharge resulting in first-time AH diagnosis, all following hospital contacts resulting in an alcohol abuse diagnosis were registered. To ensure that we only recorded new episodes of AH, we began follow-up 180 days after discharge. These patients together with the patients with recurrent AH were categorized together as continued harmful drinkers.

RESULTS
Below follows a summary of the main results from the three studies.

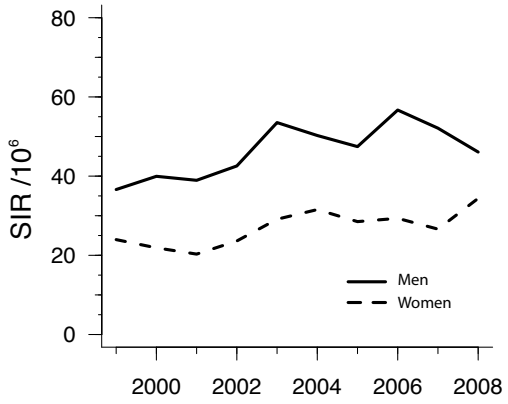
Alcoholic hepatitis cohort

We identified 1951 patients with AH, of whom 63% were men. The age of the patients ranged from 17 to 89 years; the median age increased during the study period from 48 to 55 years (The cohort is described in detail in Study I, Table 1).

Incidence and mortality (Study I)

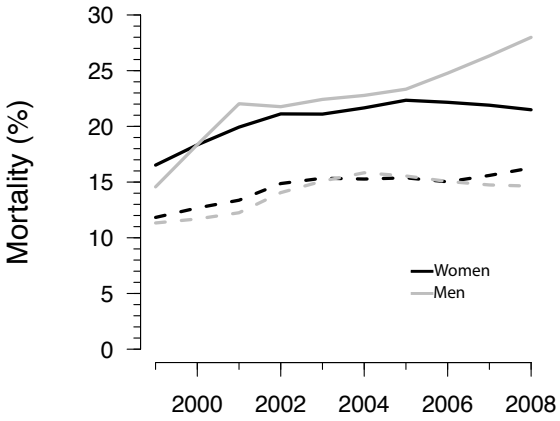
In Study I, we used the entire cohort to compute incidence and mortality rates as described above. The overall incidence rate for the study period was 36.6 per million per year (26.9 for women and 46.4 for men). As shown in Figure 3, the incidence rate rose for both men and women during the decade, and the increase was seen only in the population aged 45 years or older and was most prominent among women.

Figure 3. Standardised incidence rate per million per year, 1999–2008.



In addition to an increasing incidence, our study also showed an increasing short-term mortality for patients with AH. As illustrated in Figure 4, the 28-day and 84-day mortality increased for both men and women. The observed increase in short-term mortality was a result of confounding by increasing age and prevalence of cirrhosis because there was no increase in short-term mortality after adjustment for age, sex, and cirrhosis (adjusted hazard ratio 1.30, 95% CI 0.90–1.88). The overall 5-year mortality was 56%, and the 10-year mortality was 72%, and a concurrent diagnosis of cirrhosis had a high impact on the long-term mortality.

Figure 4. Twenty-eight-day (dashed line) and 84-day mortality (full line), 1999– 2008.

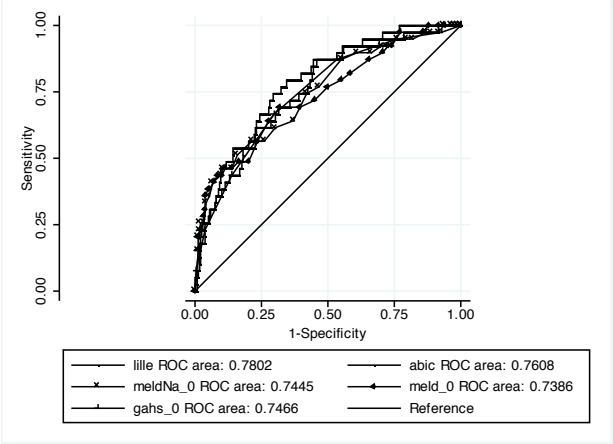


Validation of prognostic scores (Study II)

In Study II, we identified all the patients in the original cohort where laboratory data was available. The total number of patients included was 274. In this fraction of the original cohort, the 28-day mortality was 16%, and 84-day mortality 27%. This was comparable to the entire cohort (overall 28-day mortality 15% and 84-day mortality 22%).

The AUROCs for 28-day mortality were between 0.74 and 0.78, and there were no statistically significant differences among the models (p = 0.85) (Figure 5). For 84-day mortality there was still no statistically significant difference between the models (p = 0.37) and the AUROCs were between 0.69 and 0.77

Figure 5. Receiver operating curve of all scores on admission, used to predict mortality at 28 days



After the initial ROC analysis, we used the cut-offs specified in Table 2 to calculate the positive and negative predictive values for death, as well as the sensitivity and specificity for each model. The models' rates of correct prediction of death (PPVs) were low (<30%), and their rates of false prediction of death (NPVs) were high (>90%) for 28-day mortality, as assessed on admission. Detailed tables of these results can be found in Study II.

Causes of death (Study III)

In Study III, we identified all the deceased patients in the original cohort.

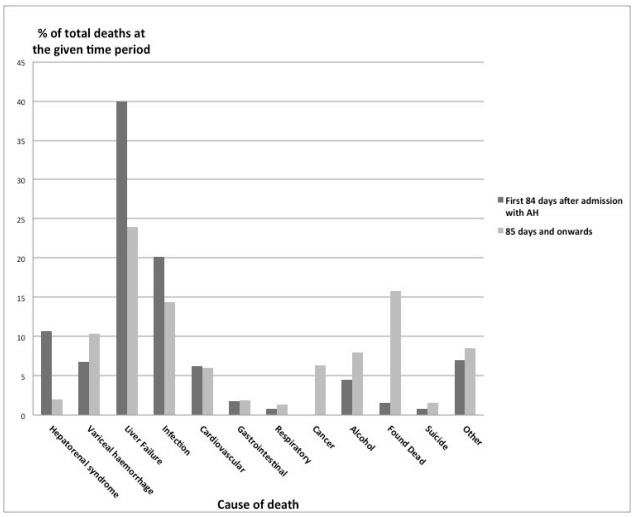
Of the 1951 patients in the original cohort, 1001 patients (364 women, 637 men) died at a median age of 54 years. As described above, the patients were stratified into two categories according to the survival time after diagnosis, to distinguish between causes of death related to the acute episode of AH and causes of death after recovery from AH. In all, 401 patients died within the first 84 days after admission for AH, and 600 patients died later.

Causes of death in acute alcoholic hepatitis and after recovery

During the first 84 days, liver-related events were the most frequent cause of death: liver failure (40%) hepato-renal syndrome (HRS) (11%), and variceal haemorrhage (7%) (Figure 6). Infections caused 20% of the deaths. After day 84, liver-related events remained the largest contributor to death (36%), and the fraction of patients that died from infections declined to 14%. Cancer was only present as a cause of death after 84 days and accounted for 6% of the deaths in this category. A very large percentage, 16% (n = 95) of the deceased were "found dead".

The distributions of causes of death before and after 84 days following admission for AH were statistically significantly different ($p < 0.001$). Our analysis of the impact of the chosen hierarchy showed that changing the hierarchy of the ranks did not affect the overall distribution of causes of death ($p = 0.95$).

Figure 6. Distribution of the causes of death according to the time since admission for AH



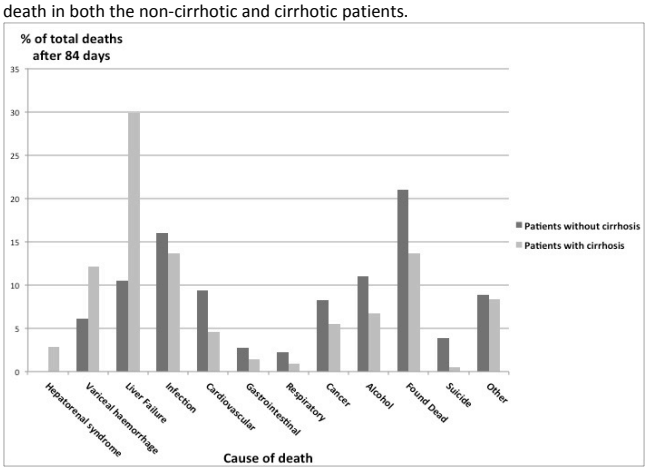
Cirrhosis

For patients who did not have concurrent cirrhosis, the 10-year risk of developing cirrhosis was 24%. Cirrhosis at the time of AH diagnosis did not affect the short-term causes of death, but long-term, liver-related deaths were more frequent in the patients who had cirrhosis than those who did not (Figure 7).

Continued harmful drinking

Following discharge with a first time AH diagnosis, the ten-year risk of having a hospital contact because of harmful drinking was 51.8%. There was no difference between the causes of death in patients with continued harmful drinking compared to the other patients ($p=0.055$) but harmful drinking increased the incidence rate of cirrhosis by a factor of 2.

Figure 7. Distribution of the long-term (>84 days since admission for AH) causes of death in both the non-cirrhotic and cirrhotic patients.



DISCUSSION

Design

The epidemiologic register-based cohort study design has its inherent strengths and weaknesses that must be taken into account when interpreting the results. One main strength is that because the Danish registers are close to 100% complete we are able to obtain a large patient material with complete follow-up. This allows us to make accurate estimates on incidence and prognosis as well as to perform time-trend analysis. Furthermore, the cohort design can assess the relationship between an exposure and several outcomes. The population-based design eliminates the potential problem of bias associated with referrals to a specific hospital. As a consequence, the design has high external validity, which makes it possible to compare the results to other cohorts (countries), providing difference between the cohorts is kept in mind. The design is limited by the amount of data available depending on the databases applied. This limits the exposures and confounders that can be studied and thus the questions that can be answered.

Lack of knowledge of individual level alcohol consumption is a central limitation of the epidemiologic register-based cohort study design. In the investigation of AH, detailed knowledge of alcohol consumption is of obvious interest. Ideally, individual level data on alcohol history would have enabled us to answer several important questions about the impact of alcohol consumption leading up to admission as well as the impact of alcohol consumption on risk of AH relapse and death after discharge. However, a complete detailed alcohol history of nearly 2000 patients (or a large subgroup) would require carefully designed questionnaires and meticulous data management outside the scope and possibilities of these studies. When investigating the causes of death in study 3, we choose to identify the patients re-admitted with discharge diagnosis related to excessive alcohol consumption. This approach identifies the patients with the most severe continued alcohol use after discharge, but it does not identify the effects of alcohol in the other patients. Furthermore this method is subject to selection bias as it includes only patients who live long enough to be re-admitted.

In the design of Study II we chose to evaluate all the scores in the same cohort. As mentioned, the prognostic models have all been created in different patient cohorts. The argument can be made that it would have been better to validate the models in cohorts similar to those in which they were developed; the Lille score (for example) in the subset of patients in the Danish registry that received steroids or the ABIC score in those with biopsy-proved AH and so on. In clinical practice, however, it is unrealistic to expect that physicians will use up to five different scoring systems depending on the best fit of their patient to the original cohorts. Much more likely, physicians will choose one (or two) model(s) and use it (them) for all their patients. In other words, a prediction model needs to be validated in the cohort for which it is to be used. A more recent study has evaluated five scores (Child-Pugh, MELD, mDF, GAHS, and ABIC score) in 44 biopsy proven patients with AH and reached similar results and conclusions as our study.(65)

The studies in the thesis are by nature observational and there is no intervention/experimental control that in the strict sense can make it possible to test a priori hypotheses. Nonetheless, the studies were driven by number of expectations – for example in

paper I that there is a temporal increase in incidence, and the data seem to reject that there was no change; in paper II the expectation mostly was that the scores performed the same way, which was not rejected by the data; in paper III we primarily expected the short- and long-term distributions of causes of death to be different and data showed they were.

Bias

Loss to follow-up is a potential source of selection bias in cohort studies, but because the registry we used to obtain data on death is complete, the loss to follow-up in our studies in negligible. Another source of bias for all our three studies is that we rely on the discharge diagnosis as entered in the national registry of patients by the discharging physician. As mentioned, the diagnosis of AH is not based on detailed or established diagnostic criteria, which will result in a certain amount of misclassified patients, and thus to bias, as will the unavoidable random errors in registration. As stated, all 3 papers rely on the validity of the AH discharge diagnosis and consequently, misclassification is a cause of concern. However, the diagnoses registered in the National Registry can generally be assumed to have a high validity, and no new diagnostic criteria or methods have been introduced during our study period.(66, 67) Consequently, we assume that there was no drift in diagnostic validity in the study period that could have disrupted our time-trend analysis. Despite the misclassifications it is worth to note that the registry diagnoses identified a patient cohort with markedly distinct clinical course compared to the background. Still, we could have improved our studies if we had performed an internal validation of the diagnosis in the NRP by reviewing a number of patient cases and confirming the diagnosis of AH.

In Study I, diagnostic inaccuracy may have lead to the incidence and mortality of AH being over- or underestimated, but we do not believe that such inaccuracy can produce the time trends we found. In Study II, if we included a fraction of patients with trivial disease and thus the wrong diagnosis, this could have led to lower AUROCs than expected. If so, our reported AUROCs could be underestimated. For Study III, if a fraction of the patients with AH in reality had end-stage cirrhosis, this might have led to bias towards an overestimation of liver failure as a cause of death.

Another weakness of our study design is the lack of individual data regarding treatment and disease severity. Because of the nature of the population-based design, the study cohort included both patients that received treatment (severe AH) and patients that did not. For Studies I and III, this affects the way the reader should interpret the results. The incidence is not dependent on treatment, but the mortality figures are thus average mortality rates for patients with AH of all severities, treated by specialists. Treatment, although none of them definitely demonstrated to be efficient regarding mortality, may have an effect on the causes of death, and consequently, the causes we identified in Study III can help focus on areas that need attention even when patients receive treatment.

In Study II, our cohort's mortality includes the possible effects of treatment of some patients and might have been higher without such treatment. This is in contrast to the development of the GAHS model in which the patients received no treatment.(46) However, we also found lower AUROCs with the other models than in the original cohorts in which patients were treated according to their Maddrey DF. Therefore, treatment effects were probably not the primary cause for the lower AUROC's we found in our cohort.

In Study II we only included patients with AH who had laboratory data available, thus making calculation of the clinical scores possible. This selection could potentially threaten the generalisability of our results if the patients who had laboratory data were also (for example) those with the most severe disease. However, such selection is unlikely because the availability of the laboratory data was only dependant on database infrastructure, not on AH severity.

Confounding

In contrast to bias, which is a consequence of the study design and cannot be accounted for during data analysis, it is possible to adjust for known or suspected confounding factors provided the data on the factors is available. In Study I, our analyses indicated that the increasing short-term mortality was well explained by confounding by cirrhosis and older age. Naturally, age had an influence on causes of death in Study III, whereas gender did not. For Studies I–III, there may also have been secular changes in the prevalence of co-morbidity. It is a limitation of our register-based design that we did not have individual-level data on co-morbidity. Co-morbidity may have increased and been part of the effects of older age since co-morbidity is a prognostic factor for patients with alcoholic cirrhosis(17). Finally, we believe that changes in drinking patterns, both binge-drinking and total quantity, are very important for the development and mortality of AH and may explain our findings of increasing incidence.

External data sources

We have used alcohol consumption data from national databases on alcohol sale, and large national surveys to try to interpret some of our findings in study I. This approach allows us to assess our results in relation to general tendencies in Denmark, but there is no individual-link between the national alcohol taxation databases and our data. In the study period, overall annual per-capita sales of pure alcohol fell by 13% and the fraction of Danes with potentially harmful drinking increased for both men and women(68, 69). In Study I we found that the incidence of AH in Denmark has increased from 1999-2008. The patients are older at diagnosis and more have cirrhosis, resulting in worse short-term prognosis. No other population-based studies on the incidence of AH exist, but our findings are in concordance with previous studies.(70) The increase in incidence observed in our study likely reflects these changes in drinking patterns, although there may be a risk of bias from changes in diagnostic methods and in the validity of the diagnosis as mentioned above. However, such changes would have the same effect on the incidence rate in all gender- and age-categories, but we found that the incidence increase was seen only above age 45 years, and primarily among women. Both the total alcohol sale and the percentage of heavy drinkers have declined in the latest public survey conducted after our study, and it will be interesting to see if the incidence of AH follows this trend(71).

CONCLUSIONS

We found an increasing incidence of AH in the Danish population during the period 1998–2008. The short-term mortality rose, attributable to older patient age and higher co-occurrence of cirrhosis. The long-term prognosis was dismal, particularly in the presence of cirrhosis.

The MELD, the MELD-Na, the GAHS, the Lille-model, and the ABIC score each and to the same degree predicted the mortality of our

patients with AH. The models may be helpful adjuvants in the routine management of patients, provided that clinicians are aware of the models' limitations.

The causes of death in AH are due to short- and long-term liver-related complications. This finding may suggest that patients with AH would benefit from continued follow-up after the acute episode. The focus should be on achieving abstinence from alcohol and on treating infections and the complications of cirrhosis.

FUTURE PERSPECTIVES

We have shown that the incidence of AH is increasing despite a decline in total alcohol consumption in Denmark. This development is a cause of concern and should be watched.

To counsel patients with AH and for strata in clinical trials, we need more accurate prediction models. This is well illustrated by the current debate regarding liver transplantation in AH. The predictive information to be gained by pragmatically combining routine laboratory tests into different formulas has been exhausted. Future scoring systems should take into account the pathophysiology of AH because of the inflammatory nature of AH, and the introduction of new immunological markers could be promising.

The increasing incidence combined with the unchanging dismal prognosis confirms the fact that we haven't seen any leaps forward in terms of treatment of AH. This emphasises the need for a deeper pathophysiological understanding of the disease and for more basic research in AH, in order to identify new targets for treatment. Our group aim to contribute to this area, and we are therefore currently conducting research into the immunopathology in AH.

Liver-related disease was the leading cause of short- and long-term death in patients with AH, and patients have a high risk of developing cirrhosis following the first admission for AH. Combined with the high 5-year mortality, we found in Study I, this poses the interesting question whether patients with AH would benefit from continued follow-up by hepatologists in an outpatient setting.

It is an important finding that many AH patients died from liver-related causes, although they survived the acute AH episode and presumably recovered from the inflammatory condition. This finding indicates the presence of a chronic liver problem, such as cirrhosis or continuous alcoholic liver damage, or that the acute episode may have left the liver conditioned for further damage. Future studies are needed to address this issue.

The Danish Health Care system and the comprehensive registers unambiguously linked by the CRS database have proven a valuable resource for conducting high quality clinical epidemiological studies. Further studies in patients with AH by cross linkage of these databases could answer questions on prognosis after surgery and adherence to medical therapy. Furthermore, in the future we will hopefully be able to measure the impact of new treatments on short- and long-term mortality.

SUMMARY

Alcoholic hepatitis (AH) is an acute inflammatory syndrome causing significant morbidity and mortality. The prognosis is strongly dependent on disease severity, as assessed by clinical scoring systems. Reliable epidemiological data as well as knowledge of the clinical course of AH are essential for planning and resource allocation within the health care system. Likewise, individual evaluation of risk is desirable in the clinical handling of patients with AH as it can guide treatment, improve patient information, and serve as strata in clinical trials.

The present Ph.D. thesis is based on three studies using a cohort of nearly 2000 patients diagnosed with AH in Denmark from 1999 to 2008 as a cohort, in a population-based study design.

The aims of this thesis were as follows. (1) To describe the incidence and short- and long-term mortality, of AH in Denmark (Study I). (2) To validate and compare the ability of the currently available prognostic scores to predict mortality in AH (Study II). (3) To investigate the short- and long-term causes of death of patients with AH (Study III).

During the study decade, the annual incidence rate in the Danish population rose from 37 to 46 per 106 for men and from 24 to 34 per 106 for women. Both short- and long-term mortality rose for men and women, and the increase in short-term mortality was attributable to increasing patient age and prevalence of cirrhosis.

Our evaluation of the most commonly used prognostic scores for predicting the mortality of patients with AH showed that all scores performed similarly, with Area under the Receiver Operator Characteristics curves giving values between 0.74 and 0.78 for 28-day mortality assessed on admission.

Our study on causes of death showed that in the short-term (<84 days after diagnosis), patients with AH were likely to die from liver-related events and infections. In the long-term (≥84 days after diagnosis), those who developed cirrhosis mainly died from liver-related causes, and those who did not develop cirrhosis mainly died from causes related to alcohol abuse.

In conclusion, the present thesis provides novel warranted epidemiological information about AH that shows increasing incidence and mortality rates. Consequently, it reiterates the fact that AH is a life-threatening disease and suggests that AH is an increasing public health concern. The most widely used prognostic models may be helpful adjuvants in the routine management of patients with AH, provided that clinicians are aware of the models' limitations.

The causes of death in AH are primarily due to liver-related complications, suggesting that patients with AH could benefit from continued follow-up by a hepatologist after the acute episode.

References

1. WHO. Global status report on alcohol and health. 2011.
2. Statistics Denmark. In: http://www.statistikbanken.dk.
3. Boniol M, Autier P. Prevalence of main cancer lifestyle risk factors in Europe in 2000. Eur J Cancer 2010;46:2534-2544.
4. Hansen AB, Hvidtfeldt UA, Gronbaek M, Becker U, Nielsen AS, Tolstrup JS. The number of persons with alcohol problems in the Danish population. Scand J Public Health 2011;39:128-136.
5. Rabinovich L, Brutscher P, Vries H, Tiessen J, Clift J, Reding A. The affordability of alcoholic beverages in the European Union. Technical Report by the European Commission 2009.
6. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease

and injury and economic cost attributable to alcohol use and alcohol-use disorders. Lancet 2009;373:2223-2233.
7. Corrao G, Ferrari P, Zambon A, Torchio P. Are the recent trends in liver cirrhosis mortality affected by the changes in alcohol consumption? Analysis of latency period in European countries. J Stud Alcohol 1997;58:486-494.
8. Mann RE, Smart RG, Anglin L, Adlaf EM. Reductions in cirrhosis deaths in the United States: associations with per capita consumption and AA membership. J Stud Alcohol 1991;52:361-365.
9. Baraona E, Lieber CS. Effects of ethanol on lipid metabolism. J Lipid Res 1979;20:289-315.
10. You M, Fischer M, Deeg MA, Crabb DW. Ethanol induces fatty acid synthesis pathways by activation of sterol regulatory element-binding protein (SREBP). J Biol Chem 2002;277:29342-29347.
11. Teli MR, Day CP, Burt AD, Bennett MK, James OF. Determinants of progression to cirrhosis or fibrosis in pure alcoholic fatty liver. Lancet 1995;346:987-990.
12. Becker U, Deis A, Sorensen TI, Gronbaek M, Borch-Johnsen K, Muller CF, Schnohr P, et al. Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. Hepatology 1996;23:1025-1029.
13. Bellentani S, Saccoccio G, Costa G, Tiribelli C, Manenti F, Sodde M, Saveria Croce L, et al. Drinking habits as cofactors of risk for alcohol induced liver damage. The Dionysos Study Group. Gut 1997;41:845-850.
14. Lefkowitch JH. Morphology of alcoholic liver disease. Clin Liver Dis 2005;9:37-53.
15. Jepsen P, Ott P, Andersen PK, Sorensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. Hepatology 2010;51:1675-1682.
16. Pessione F, Ramond MJ, Peters L, Pham BN, Batel P, Rueff B, Valla DC. Five-year survival predictive factors in patients with excessive alcohol intake and cirrhosis. Effect of alcoholic hepatitis, smoking and abstinence. Liver Int 2003;23:45-53.
17. Jepsen P, Vilstrup H, Andersen PK, Lash TL, Sørensen HT. Comorbidity and survival of Danish cirrhosis patients: A nationwide population-based cohort study. Hepatology 2008;48:214-220.
18. Mathurin P, Beuzin F, Louvet A, Carrie-Ganne N, Balian A, Trinchet JC, Dalsoglio D, et al. Fibrosis progression occurs in a subgroup of heavy drinkers with typical histological features. Aliment Pharmacol Ther 2007;25:1047-1054.
19. Lelbach WK. Epidemiology of alcoholic liver disease. Prog Liver Dis 1976;5:494-515.
20. Louvet A, Naveau S, Abdelnour M, Ramond MJ, Diaz E, Fartoux L, Dharancy S, et al. The Lille model: A new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. Hepatology 2007;45:1348-1354.
21. Forrest EH, Morris AJ, Stewart S, Phillips M, Oo YH, Fisher NC, Haydon G, et al. The Glasgow alcoholic hepatitis score identifies patients who may benefit from corticosteroids. Gut 2007;56:1743-1746.
22. Mathurin P, Lucey MR. Management of alcoholic hepatitis. Journal of Hepatology 2012;56 Suppl 1:S39-45.
23. Mookerjee RP, Lackner C, Stauber R, Stadlbauer V, Deheragoda M, Aigelsreiter A, Jalan R. The role of liver biopsy in the diagnosis and prognosis of patients with acute deterioration of alcoholic cirrhosis. J Hepatol 2011;55:1103-1111.
24. Forrest EH, Gleeson D. Is a liver biopsy necessary in alcoholic hepatitis? J Hepatol 2012;56:1427-1428; author reply 1428-1429.
25. Borowsky SA, Strome S, Lott E. Continued heavy drinking and survival in alcoholic cirrhotics. Gastroenterology 1981;80:1405-1409.
26. Sidhu SS, Goyal O, Singla M, Bhatia KL, Chhina RS, Sood A. Pentoxifylline in severe alcoholic hepatitis: a prospective, randomised trial. J Assoc Physicians India 2012;60:20-22.
27. Phillips M, Curtis H, Portmann B, Donaldson N, Bomford A, O'Grady J. Antioxidants versus corticosteroids in the treatment of severe alcoholic hepatitis--a randomised clinical trial. J Hepatol 2006;44:784-790.
28. Bird GL, Prach AT, McMahon AD, Forrest JA, Mills PR, Danesh BJ. Randomised controlled double-blind trial of the calcium channel antagonist amlodipine in the treatment of acute alcoholic hepatitis. J Hepatol 1998;28:194-198.
29. Moreno C, Langlet P, Hittelet A, Lasser L, Degre D, Evrard S, Colle I, et al. Enteral nutrition with or without N-acetylcysteine in the treatment of severe acute alcoholic hepatitis: a randomized multicenter controlled trial. J Hepatol 2010;53:1117-1122.
30. De BK, Gangopadhyay S, Dutta D, Baksi SD, Pani A, Ghosh P. Pentoxifylline versus prednisolone for severe alcoholic hepatitis: a randomized controlled trial. World J Gastroenterol 2009;15:1613-1619.
31. Boetticher NC, Peine CJ, Kwo P, Abrams GA, Patel T, Aqel B, Boardman L, et al. A Randomized, Double-Blinded, Placebo-Controlled Multicenter Trial of Etanercept in the Treatment of Alcoholic Hepatitis. Gastroenterology 2008;135:1953-1960.
32. Stewart S, Prince M, Bassendine M, Hudson M, James O, Jones D, Record C, et al. A randomized trial of antioxidant therapy alone or with corticosteroids in acute alcoholic hepatitis. J Hepatol 2007;47:277-283.
33. Naveau S, Chollet-Martin S, Dharancy S, Mathurin P, Jouet P, Piquet MA, Davion T, et al. A Double-Blind Randomized Controlled Trial of Infliximab Associated with Prednisolone in Acute Alcoholic Hepatitis. Hepatology 2004;39:1390-1397.
34. Mezey E, Potter JJ, Rennie-Tankersley L, Caballeria J, Pares A. A randomized placebo controlled trial of vitamin E for alcoholic hepatitis. J Hepatol 2004;40:40-46.
35. Ramond MJ, Poynard T, Rueff B, Mathurin P, Theodore C, Chaput JC, Benhamou JP. A randomized trial of prednisolone in patients with severe alcoholic hepatitis. N Engl J Med 1992;326:507-512.
36. Mezey E, Caballeria J, Mitchell MC, Pares A, Herlong HF, Rodes J. Effect of parenteral amino acid supplementation on short-term and long-term outcomes in severe alcoholic hepatitis: a randomized controlled trial. Hepatology 1991;14:1090-1096.
37. Bonkovsky HL, Fiellin DA, Smith GS, Slaker DP, Simon D, Galambos JT. A randomized, controlled trial of treatment of alcoholic hepatitis with parenteral

nutrition and oxandrolone. I. Short-term effects on liver function. Am J Gastroenterol 1991;86:1200-1208.
38. Bird G, Lau JY, Koskinas J, Wicks C, Williams R. Insulin and glucagon infusion in acute alcoholic hepatitis: a prospective randomized controlled trial. Hepatology 1991;14:1097-1101.
39. Trinchet JC, Beaugrand M, Callard P, Hartmann DJ, Gotheil C, Nusgens BV, Lapiere CM, et al. Treatment of alcoholic hepatitis with colchicine. Results of a randomized double blind trial. Gastroenterol Clin Biol 1989;13:551-555.
40. Carithers RL, Jr., Herlong HF, Diehl AM, Shaw EW, Combes B, Fallon HJ, Maddrey WC. Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicenter trial. Ann Intern Med 1989;110:685-690.
41. Simon D, Galambos JT. A randomized controlled study of peripheral parenteral nutrition in moderate and severe alcoholic hepatitis. J Hepatol 1988;7:200-207.
42. Achord JL. A prospective randomized clinical trial of peripheral amino acid-glucose supplementation in acute alcoholic hepatitis. Am J Gastroenterol 1987;82:871-875.
43. Baker AL, Jaspan JB, Haines NW, Hatfield GE, Krager PS, Schneider JF. A randomized clinical trial of insulin and glucagon infusion for treatment of alcoholic hepatitis: progress report in 50 patients. Gastroenterology 1981;80:1410-1414.
44. Blitzer BL, Mutchnick MG, Joshi PH, Phillips MM, Fessel JM, Conn HO. Adrenocorticosteroid therapy in alcoholic hepatitis. A prospective, double-blind randomized study. Am J Dig Dis 1977;22:477-484.
45. Maddrey WC, Boitnott JK, Bedine MS. Corticosteroid therapy of alcoholic hepatitis. Gastroenterology 1978;75:193-199.
46. Forrest EH, Evans CDJ, Stewart S, Phillips M, Oo YH, McAvoy NC, Fisher NC, et al. Analysis of factors predictive of mortality in alcoholic hepatitis and derivation and validation of the Glasgow alcoholic hepatitis score. Gut 2005;54:1174-1179.
47. Dunn W, Jamil LH, Brown LS, Wiesner RH, Kim WR, Menon KVN, Malinchoc M, et al. MELD accurately predicts mortality in patients with alcoholic hepatitis. Hepatology 2005;41:353-358.
48. Rincon D, Lo Iacono O, Ripoll C, Gomez-Camarero J, Salcedo M, Catalina MV, Hernando A, et al. Prognostic value of hepatic venous pressure gradient for in-hospital mortality of patients with severe acute alcoholic hepatitis. Alimentary Pharmacology and Therapeutics 2007;25:841-848.
49. Dominguez M, Rincón D, Abraldes JG, Miquel R, Colmenero J, Bellot P, García-Pagán JC, et al. A new scoring system for prognostic stratification of patients with alcoholic hepatitis. American Journal of Gastroenterology 2008;103:2747-2756.
50. Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. BMJ (Clinical Research Ed.) 2009;338.
51. Mathurin P, O'Grady J, Carithers RL, Phillips M, Louvet A, Mendenhall CL, Ramond MJ, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: Meta-analysis of individual patient data. Gut 2011;60:255-260.
52. Sidhu SS, Goyal O, Singla P, Gupta D, Sood A, Chhina RS, Soni RK. Corticosteroid plus pentoxifylline is not better than corticosteroid alone for improving survival in severe alcoholic hepatitis (COPE trial). Dig Dis Sci 2012;57:1664-1671.
53. Coffin PO, Sharpe BA. Cause of death in alcoholic hepatitis. J Hosp Med 2007;2:51-52.
54. Sandahl TD, Jepsen P, Thomsen KL, Vilstrup H. Incidence and mortality of alcoholic hepatitis in Denmark 1999-2008: a nationwide population based cohort study. Journal of Hepatology 2011;54:760-764.
55. Liangpunsakul S. Clinical characteristics and mortality of hospitalized alcoholic hepatitis patients in the United States. J Clin Gastroenterol 2011;45:714-719.
56. Verma S, Ajudia K, Mendler M, Redeker A. Prevalence of septic events, type 1 hepatorenal syndrome, and mortality in severe alcoholic hepatitis and utility of discriminant function and MELD score in predicting these adverse events. Dig Dis Sci 2006;51:1637-1643.
57. Louvet A, Wartel F, Castel H, Dharancy S, Hollebecque A, Canva-Delcambre V, Deltenre P, et al. Infection in patients with severe alcoholic hepatitis treated with steroids: early response to therapy is the key factor. Gastroenterology 2009;137:541-548.
58. O'Keefe JH, Bybee KA, Lavie CJ. Alcohol and cardiovascular health - The razor-sharp double-edged sword. J Am Coll Cardiol 2007;50:1009-1014.
59. Romelsjo A, Stenbacka M, Lundberg M, Upmark M. A population study of the association between hospitalization for alcoholism among employees in different socio-economic classes and the risk of mobility out of, or within, the workforce. Eur J Public Health 2004;14:53-57.
60. Frank L. Epidemiology. When an entire country is a cohort. Science 2000;287:2398-2399.
61. Pedersen CB. The Danish Civil Registration System. Scand J Public Health 2011;39:22-25.
62. Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. Dan Med Bull 2006;53:441-449.
63. Grann AF, Erichsen R, Nielsen AG, Froslev T, Thomsen RW. Existing data sources for clinical epidemiology: The clinical laboratory information system (LABKA) research database at Aarhus University, Denmark. Clin Epidemiol 2011;3:133-138.
64. Helweg-Larsen K. The Danish Register of Causes of Death. Scand J Public Health 2011;39:26-29.
65. Palaniyappan N, Subramanian V, Ramappa V, Ryder SD, Kaye P, Aithal GP. The utility of scoring systems in predicting early and late mortality in alcoholic hepatitis: whose score is it anyway? Int J Hepatol 2012;2012:624675.
66. Andersen TF, Madsen M, Jørgensen J, Mellemkjær L, Olsen JH. The Danish National Hospital Register: A valuable source of data for modern health sciences. Danish Medical Bulletin 1999;46:263-268.
67. Vestberg K, Thulstrup AM, Sorensen HT, Ottesen P, Sabroe S, Vilstrup H. Data quality of administratively collected hospital discharge data for liver cirrhosis epidemiology. J Med Syst 1997;21:11-20.
68. lindeskov C. News from Statistisk Denmark on alcohol consumption

URL:http://www.dst.dk/pukora/epub/nyt/2009/NR321.pdf. 2008;321.
69. Ekholm O, Kjøller M, Davidsen M, Hesse U, Eriksen L, Christensen AL, Grønbæk M. Health and disease development in Denmark form 1987 to 2005: National institute of public health, Denmark URL:http://www.si-folkesundhed.dk/upload/hele_rapporten_2005.pdf; 2006.
70. Yang AL, Vadhavkar S, Singh G, Omary MB. Epidemiology of alcohol-related liver and pancreatic disease in the United States. Archives of Internal Medicine 2008;168:649-656.
71. Illemann A, Ekholm O, Davidsen M, Juel K. Health and disease development in Denmark form 1987 to 2010: National institute of public health, Denmark URL:http://http://www.si-folkesundhed.dk/upload/sundhed_og_sygelighed_2010,_med_sidetal.pdf; 2006.