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Incidence and prognosis of tuberculosis in patients with cirrhosis of the liver. A Danish nationwide population based study

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SUMMARY

We examined the incidence rate and prognosis of tuberculosis in a cohort of patients with liver cirrhosis in Denmark. In a study cohort of 22675 patients with liver cirrhosis, we identified 151 cases of tuberculosis from 1977 to 1993. The incidence rate was 168·6 per 100000 person-years of risk, and the highest incidence rate was among men above 65 years of age, with an incidence rate of 246·0 per 100000 person-years of risk. The 30-day case-fatality rate was 27·3% and the 1-year case fatality rate was 47·7%. The results demonstrate that patients with liver cirrhosis are at increased risk of tuberculosis. Additionally, it is suggested that liver cirrhosis is an independent risk factor for tuberculosis, and that patients with liver cirrhosis who acquire tuberculosis have a poor prognosis.

INTRODUCTION

The decline in incidence and mortality of tuberculosis began in the middle of the last century, but in many Western countries notifications of tuberculosis have increased during the last 10 years [1–4]. Tuberculosis is often associated with poverty, immigration, homelessness, overcrowding at the household level or HIV infections [2, 5, 6]. The association between tuberculosis and alcohol abuse is also well known due to impaired immune responses [1, 7].

Protective immunity against tuberculosis depends mainly on the delayed cellular hypersensitivity response [8, 9]. However, when tuberculin-tested after several months of alcohol abstinence, patients with alcoholic liver cirrhosis often remain cutaneously anergic and demonstrate impairment of the delayed cellular hypersensitivity response [10].

Thus, liver cirrhosis in itself may be a risk factor for development of tuberculosis, independent of alcohol abuse. Furthermore, patients with liver cirrhosis often suffer from malnutrition which contributes to immune deficiency [11].

On this background, we examined the incidence rate and the 30-day and 1-year case-fatality rates of tuberculosis in a nationwide cohort of patients with liver cirrhosis in Denmark.

PATIENTS AND METHODS

The study was conducted in Denmark, which has approx. 5·2 million inhabitants. Every Danish resident is assigned a personal identification number (CPR number) shortly after birth or at immigration, in which date of birth and gender are incorporated. The study cohort was identified in the Danish National Registry of Patients (NRP), which contains information on all hospital admissions since 1977 and covers 99·9% of all discharges from somatic departments in the country [12]. Each admission record includes CPR number, date of admission, date of

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Table 1. *Characteristics of 22675 patients with liver cirrhosis in Denmark 1977–93*

	Women	Men	All
No. of patients	8510	14165	22675
Proportion with alcoholic cirrhosis (%)	45·4	70·3	60·9
No. of cases with TB	38	113	151·0
Total person-years	36718	52850	89568
Mean follow-up (years)	4·3	3·7	4·0

Table 2. *The incidence rate (IR) and 95% confidence interval (CI) of tuberculosis among patients with liver cirrhosis according to age, gender and type of cirrhosis*

Gender	Age (years)	No. of cases	Person-years at risk	IR	95% CI
Women	⩽ 50	5	8608	58·1	18·8–135·6
Men	⩽ 50	35	18464	189·6	132·0–263·6
Women	50–65	14	14274	98·1	53·6–164·6
Men	50–65	47	21785	215·7	158·5–286·9
Women	⩾ 65	19	13836	137·3	82·7–214·4
Men	⩾ 65	31	12601	246·0	167·1–349·2
Non-alcoholic cirrhosis	—	53	31682	167·3	125·3–218·8
Alcoholic cirrhosis	—	111	57886	191·8	157·7–230·9
Women (all)	—	38	36718	103·5	73·2–142·1
Men (all)	—	113	52850	213·8	176·2–257·1

discharge, and up to 20 discharge diagnoses. Diagnoses were classified according to the Danish version of the International Classification of Diseases, 8th edition (ICD-8), during the study period [13]. Patients were included in the study when they had been discharged at least once with a diagnosis of liver cirrhosis (ICD-8 = 571·09, 571·90, 571·92, 571·93, 571·99) from 1 January 1977 until 31 December 1993. We included only patients above 20 years of age in the cohort, since children often have inborn errors of metabolism or malformations as the aetiological factor for liver cirrhosis. Patients were stratified into two sub-cohorts, one consisting of patients discharged with a diagnosis of alcoholic liver cirrhosis (ICD-8 = 571·09) and the other consisting of patients with a diagnosis of non-alcoholic liver cirrhosis (ICD-8 = 571·90, 571·92, 571·93, 571·99). To reduce misclassification, patients discharged with a diagnosis of alcoholism (ICD-8 = 303) at any time from 1977 to 1993 were always referred to the sub-cohort of alcoholic liver cirrhosis, no matter which cirrhosis code was registered.

Patients with liver cirrhosis were registered as having an episode of tuberculosis if discharged with a diagnosis of tuberculosis with no regard to location (ICD-8 = 0·10·00–018·99). All patients with a diagnosis of tuberculosis prior to a diagnosis of liver cirrhosis, as well as patients with the diagnosis tuberculosis sequela (ICD-8 = 0·19·00–0·19·99), were excluded.

We obtained information on vital status from the Central Personal Registry (CPR), which has kept electronic records of all changes in vital status such as date of emigration and date of death since 1968.

STATISTICAL ANALYSIS

The follow-up period for tuberculosis began at the date of discharge from the hospital with liver cirrhosis, irrespective of cirrhosis type, and ended at the date of discharge with a diagnosis of tuberculosis, date of death or 31 December 1993, whichever occurred first. Patients who were diagnosed with liver cirrhosis and tuberculosis during the same admission were included as cases and registered as zero person-years at risk.

The incidence rate was calculated as the number of cases divided by the person-years at risk for each age group, gender or type of cirrhosis, and the 95% confidence intervals (95% CIs) were estimated according to Fisher's exact limits [14].

We used logistic regression analysis to estimate the association between tuberculosis and 30-day case-fatality and 1-year case-fatality rate (deaths within 30

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days or 1 year of discharge). The cohort was divided into three age categories, less than 50 years (the reference group), between 50 and 65 years, and above 65 years, and divided according to gender, with women as the reference group.

The cohort was also divided according to type of cirrhosis, alcoholic cirrhosis and non-alcoholic cirrhosis (the reference group) and type of tuberculosis, extra-pulmonary and pulmonary tuberculosis (the reference group) [15].

RESULTS

A total of 22675 patients with liver cirrhosis were followed for a mean period of 4 years, a total of 89568 person-years. In the study cohort, 61% had alcoholic cirrhosis. There were 62% men and 38% women, and the mean age was 57·4 years when entering the study. We identified 151 cases of tuberculosis in the cohort during the study period, 113 men and 38 women. Ninety-eight of the cases (58%) had alcoholic liver cirrhosis (Table 1).

The incidence rate of tuberculosis among patients with liver cirrhosis was 168·6 per 100000 person-years. The incidence rate for men was 213·8 per 100000 person-years, compared to women with an incidence rate of 103·5 per 100000 person-years. The incidence rate increased with age in both genders and was highest in men above 65 years of age at 246·0 per 100000 person-years (Table 2).

In a recent Danish study, the incidence rate of tuberculosis in the general population in the age group 55–64 years was 8 per 100000 person-years, yielding an incidence rate ratio of 27·0 (95% CI 12·6–66·1). For women the incidence rate was 4 per 100000 for the same age group, giving an incidence rate ratio of 34·3 (95% CI 11·4–138·8).

We found a 30-day case-fatality rate of 27·3% (40/151) among the liver cirrhotic patients with tuberculosis, and the highest risk was found among patients above 65 years of age with an adjusted odds ratio of 1·68 (95% CI 0·99–2·51). Among patients with extra-pulmonary tuberculosis, 30-day case-fatality was increased with an adjusted odds ratio of 1·38 (95% CI 0·44–4·30). Case-fatality was not influenced by gender or type of cirrhosis (Table 3).

We found a 1-year case-fatality rate of 47·7% (72/151). The same trend was found with the highest risk among patients above 65 years of age, with an adjusted odds ratio of 1·59 (95% CI 1·01–2·49).

Table 3. *30-day and 1-year case-fatality among patients with liver cirrhosis after diagnosis of tuberculosis (n = 151)*

	30-day case-fatality			1-year case-fatality		
	Death/cases	Crude OR (95% CI)	Adjusted OR (95% CI)	Deaths/cases	Crude OR (95% CI)	Adjusted OR (95% CI)
Age (years)						
< 50 (reference category)	9/40	1·0	1·0	16/40	1·0	1·0
50–65	10/61	0·68(0·25–1·85)	0·64(0·23–1·79)	24/61	0·97(0·43–2·20)	0·88(0·38–2·03)
> 65	21/50	1·68(0·99–2·51)	1·66(1·01–2·71)	32/50	1·63(1·06–2·51)	1·59(1·01–2·49)
Gender						
Women (reference category)	11/38	1·0	1·0	23/38	1·0	1·0
Men	29/113	0·87(0·37–1·92)	1·02(0·41–2·55)	49/113	0·50(0·24–1·06)	0·56(0·25–1·23)
Liver cirrhosis						
Non-alcoholic (reference category)	15/53	1·0	1·0	27/53	1·0	1·0
Alcoholic	25/98	0·87(0·41–1·88)	1·46(0·60–3·54)	45/98	0·81(0·42–1·60)	1·35(0·62–2·93)
Tuberculosis						
Pulmonary (reference category)	35/136	1·0	1·0	64/136	1·0	1·0
Extra-pulmonary	5/15	1·38(0·44–4·30)	1·5(0·45–5·14)	8/15	1·23(0·44–3·74)	1·15(0·37–3·59)

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DISCUSSION

There was a high incidence rate of tuberculosis among patients with liver cirrhosis. The highest incidence was seen in men, and in patients above 65 years of age. The case-fatality was not significantly influenced by the aetiology of liver cirrhosis nor by the location of tuberculosis, but case-fatality was significantly higher among those above 65 years of age.

The incidence rate of tuberculosis in the cohort of patients with liver cirrhosis was much higher than in the general population in Denmark during the period. In 1977 the incidence rate of tuberculosis in Denmark was 10·2 per 100000 person-years. The incidence rate declined to 5·8 per 100000 person-years in 1986, then rose slowly to 7·8 in 1993. The increasing incidence rate of tuberculosis observed in the later years of the follow-up period was almost exclusively due to immigration [16, 17]. Furthermore, the incidence rate in our study among patients with liver cirrhosis was higher than in the general population as found in a Spanish and a British study [2, 6], but not as high as found in New York City, USA [18]. Previous studies have identified ethnic background, homelessness and HIV-infection as risk factors for tuberculosis [2, 18, 19], but none of these studies have identified liver cirrhosis as an important risk factor.

The 30-day and 1-year case-fatality rates estimated in our study were high compared to the findings of others who have estimated rates among different types of patient groups and in the general population [1, 19–21]. It appears that development of tuberculosis is a very serious complication in patients with liver cirrhosis.

A strength of our study was its large size both in terms of the numbers of patients with liver cirrhosis and the numbers of patients with tuberculosis. The uniformly organized health-care system in Denmark enabled us to conduct a population-based design with a complete follow-up. However, our study had some limitations. Discharge diagnoses have varied in quality but the diagnosis of liver cirrhosis had a high quality in the NRP though there was some misclassification between the different types of liver cirrhosis [22]. A weakness of our study was its lack of clinical details, especially of information on alcohol consumption, since alcohol seems to be an independent risk factor for tuberculosis independent of liver cirrhosis [1, 23]. We did not have any information on the prevalence of homelessness in our cohort.

The incidence rate of tuberculosis among patients with liver cirrhosis was high, raising the question whether this group of patients should be supported through provision of simple measures like contact tracing and dispersing of information on common signs of tuberculosis. In view of the serious prognosis for patients with liver cirrhosis who acquire tuberculosis, the clinical implication could be routine screening of this patient group when they present with unexplained symptoms.

Our study supported the hypothesis that patients with liver cirrhosis are at an increased risk of tuberculosis and that the prognosis is poor. Furthermore, the incidence rate and the prognosis among the patients with liver cirrhosis did not change significantly when stratifying on the type of cirrhosis, indicating that liver cirrhosis is a risk factor for tuberculosis independent of alcohol.

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REFERENCES

1. Borgdorff MW, Veen J, Kalisvaart NA, Nagelkerke N. Mortality among tuberculosis patients in The Netherlands in the period 1993–1995. Eur Respir J 1998; **11**: 816–20.
2. Elender F, Bentham G, Langford I. Tuberculosis mortality in England and Wales during 1982–1992: its association with poverty, ethnicity and AIDS. Soc Sci Med 1998; **46**: 673–81.
3. Wong R, Rappaport W, Witte C, et al. Risk of nonshunt abdominal operation in the patient with cirrhosis. J Am Coll Surg 1994; **179**: 412–6.
4. Bhatti N, Law MR, Morris JK, Halliday R, Moore Gillon J. Increasing incidence of tuberculosis in England and Wales: a study of the likely causes. BMJ 1995; **310**: 967–9.
5. Bland JM, Altman DG. The use of transformation when comparing two means. BMJ 1996; **312**: 1153.
6. Franco J, Blanquer R. Mortality from tuberculosis in Spain from 1970 to 1993: changes in epidemiological trends during the acquired immune-deficiency syndrome epidemic. Int J Tuberc Lung Dis 1998; **2**: 663–9.
7. Hudolin V. Tuberculosis and alcoholism. Ann NY Acad Sci 1975; **252**: 353–64.
8. Andersen P. Host responses and antigens involved in protective immunity to *Mycobacterium tuberculosis*. Scand J Immunol 1997; **45**: 115–31.
9. Schluger NW, Rom WN. The host immune response to tuberculosis. Am J Respir Crit Care Med 1998; **157**: 679–91.

10. Schirren CA, Jung MC, Zachoval R, et al. Analysis of T cell activation pathways in patients with liver cirrhosis, impaired delayed hypersensitivity and other T cell-dependent functions. Clin Exp Immunol 1997; **108**: 144–50.
11. Ledesma Castano F, Echevarria Vierna S, Lozano Polo JL, Oloriz Rivas R, Alvarez Moreno C, Pons Romero F. Interleukin-1 in alcoholic cirrhosis of the liver: the influence of nutrition. Eur J Clin Nutr 1992; **46**: 527–33.
12. Danish National Board of Health. The activity in the hospital care system. Copenhagen: National Board of Health, 1981.
13. Danish National Board of Health. Classification of diseases. Copenhagen: National Board of Health, 1976.
14. Rothman KJ, Boice JD. Epidemiologic analyses with a programmable calculator. (DHHS Publication No [NIH] 79-1649). Washington DC, US Government Printing Office, 1979.
15. Hosmer DW, Lemeshow S. Applied logistic regression, 1st ed. New York: John Wiley & Sons, 1989.
16. Poulsen S, Rønne T, Kok-Jensen A, Bauer J, Miorner H. Tuberkuloseudviklingen i Danmark 1972–1996. Ugeskr Laeger 1999; **161**: 3452–7.
17. Pedersen JT, Reusbech PA. Tuberkulose og migration Ugeskr Laeger 1999; **161**: 3440–3.
18. Friedman LN, Williams MT, Singh TP, Frieden TR. Tuberculosis, AIDS, and death among substance abusers on welfare in New York City. N Engl J Med 1996; **334**: 828–3.
19. Bakhshi SS, Hawker J, Ali S. Tuberculosis mortality in notified cases from 1989–1995 in Birmingham. Public Health 1998; **112**: 165–8.
20. Doherty MJ, Spence DP, Davies PD. Trends in mortality from tuberculosis in England and Wales: effect of age on deaths from non-respiratory disease. Thorax 1995; **50**: 976–9.
21. Kim JH, Langston AA, Gallis HA. Miliary tuberculosis: epidemiology, clinical manifestations, diagnosis, and outcome. Rev Infect Dis 1990; **12**: 583–90.
22. Vestberg K, Thulstrup AM, Sørensen 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.
23. Rao VK, Iademarco EP, Fraser VJ, Kollef MH. The impact of comorbidity on mortality following in-hospital diagnosis of tuberculosis. Chest 1998; **114**: 1244–52.