

Alcoholic Cirrhosis Increases Risk for Autoimmune Diseases: A Nationwide Registry-Based Cohort Study

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BACKGROUND & AIMS: Alcoholic cirrhosis is associated with hyperactivation and dysregulation of the immune system. In addition to its ability to increase risk for infections, it also may increase the risk for autoimmune diseases. We studied the incidence of autoimmune diseases among patients with alcoholic cirrhosis vs controls in Denmark.

METHODS: We collected data from nationwide health care registries to identify and follow up all citizens of Denmark diagnosed with alcoholic cirrhosis from 1977 through 2010. Each patient was matched with 5 random individuals from the population (controls) of the same sex and age. The incidence rates of various autoimmune diseases were compared between patients with cirrhosis and controls and adjusted for the number of hospitalizations in the previous year (a marker for the frequency of clinical examination).

RESULTS: Of the 24,679 patients diagnosed with alcoholic cirrhosis, 532 developed an autoimmune disease, yielding an overall increased adjusted incidence rate ratio (aIRR) of 1.36 (95% confidence interval [CI], 1.24–1.50). The strongest associations were with Addison's disease (aIRR, 2.47; 95% CI, 1.04–5.85), inflammatory bowel disease (aIRR, 1.56; 95% CI, 1.26–1.92), celiac disease (aIRR, 5.12; 95% CI, 2.58–10.16), pernicious anemia (aIRR, 2.35; 95% CI, 1.50–3.68), and psoriasis (aIRR, 4.06; 95% CI, 3.32–4.97). There was no increase in the incidence rate for rheumatoid arthritis (aIRR, 0.89; 95% CI, 0.69–1.15); the incidence rate for polymyalgia rheumatica decreased in patients with alcoholic cirrhosis compared with controls (aIRR, 0.47; 95% CI, 0.33–0.67).

CONCLUSIONS: Based on a nationwide cohort study of patients in Denmark, alcoholic cirrhosis is a risk factor for several autoimmune diseases.

Keywords: Epidemiology; Population-Based; Alcoholic Liver Disease; Autoimmunity.

Alcohol overuse may lead to hepatic and systemic inflammation, both resulting from toxic effects of alcohol¹ and bacterial translocation from the gut.^{2,3} The hepatic inflammation leads to fibrosis and, ultimately, cirrhosis. The systemic inflammation hyperactivates production of proinflammatory factors^{4–7} and inflammasomes,^{3,8,9} stimulates B cells to produce high levels of nonspecific immunoglobulins^{10–12} that may serve as autoantibodies,^{13–16} and disrupts clearance of immune complexes.^{17,18} The systemic immune activation also involves formation of ectopic germinal centers in which B cells undergo somatic hypermutation, but these B cells are not assigned to autoprotection¹⁹ and therefore may produce autoantibodies that could trigger an autoimmune disease.^{20–23}

Still, however, the association between alcoholic cirrhosis and the development of autoimmune diseases has not been studied systematically. The purpose of this study, therefore, was to investigate whether alcoholic cirrhosis is a risk factor for developing autoimmune diseases. The tax-funded health care system and the availability of high-quality nationwide health care

Abbreviations used in this paper: aIRR, adjusted incidence rate ratio; CI, confidence interval; IRR, incidence rate ratio; ICD-8, International Classification of Diseases 8th edition; ICD-10, International Classification of Diseases 10th edition.

registries make Denmark an ideal place to conduct such a study.

Patients and Methods

Study Population

We conducted a nationwide registry-based cohort study of all Danish citizens diagnosed with alcoholic cirrhosis between January 1, 1977, and March 1, 2010.

Data Sources

The National Patient Registry contains data from all inpatient hospitalizations since 1977, and also data from outpatient and emergency room visits since 1995.²⁴ Data include the dates of admission and discharge and the discharge diagnosis codes. From 1977 through 1993 diagnoses were coded according to the International Classification of Diseases 8th edition (ICD-8), and since 1994 diagnoses were coded according to the ICD 10th edition (ICD-10). The Danish Civil Registration System

records dates of birth, death, immigration, and emigration of all Danish citizens. Linkage of individual-level data from the registries is possible through Danish citizens' unique personal identification number.²⁵

Identification of Cirrhosis Patients

We included all Danish citizens who received their first discharge diagnosis of alcoholic cirrhosis (ICD-8, 571.09; ICD-10, K70.3) between January 1, 1977, and March 1, 2010, except for those who had been diagnosed previously with another chronic or autoimmune liver disease (ICD-8 codes: biliary cirrhosis, 571.90 and 571.91; unspecified liver cirrhosis, 571.92; nonalcoholic liver cirrhosis, 571.99; and ICD-10 codes: chronic viral hepatitis, B18.x; toxic liver disease, K71.1; chronic active hepatitis and autoimmune hepatitis, K73.2; biliary cirrhosis, K74.3, K74.4, and K74.5; and other or unspecified liver cirrhosis, K74.6), or an autoimmune disease (Table 1). The validity of the diagnosis codes reported to the National Patient Registry generally is high,²⁶ and 92% of the diagnosis codes for alcoholic cirrhosis were confirmed by liver biopsy or established

Table 1. Definition of Autoimmune Diseases

	ICD-8	ICD-10
Organ-specific autoimmune diseases		
Endocrine system		
Hashimoto's thyroiditis	245.01, 245.03	E06.3A
Graves (Basedow's) disease	242.00	E05.0
Addison's disease	255.10, 255.11	E27.1, E27.2
Gastrointestinal system		
Inflammatory bowel disease	563.01, 563.19, 569.04	K50, M07.4, K51, M07.5
Celiac disease and dermatitis herpetiformis	269.00, 693.08, 693.09	K90.0, L13.0
Pernicious anemia	281.11, 281.01, 281.08, 281.09	D51.0
Skin		
Localized lupus erythematosus	695.49	L93
Localized scleroderma	701.01, 701.08, 701.09	D94.0, L94.1, L94.3
Pemphigus foliaceus	694.02	L10.2
Pemphigoid	694.05	L12
Neuromuscular system		
Myasthenia gravis	733.09	G70.0
Central nervous system		
Multiple sclerosis	340.00, 340.01, 340.08, 340.09	G35.9
Organ nonspecific autoimmune diseases		
Connective tissue diseases		
Systemic sclerosis (scleroderma)	734.1	M34, M34.0, M34.1, M34.8
Rheumatoid arthritis	712.39, 712.59	M05, M06.0, M06.8, M06.9
Psoriasis and psoriatic arthritis	696.09, 696.10, 696.19	L40.0, L40.4, L40.5, L40.8, M40.9, M07.3
Ankylosing spondylitis (morbus Bechterew)	712.49	M45, M08.1
Polymyositis/dermatomyositis	716.09, 716.19	M33
Systemic lupus erythematosus	734.19	M32.1, M32.8, G05.8A, G73.7C, I32.8B, I39.8C, J99.1C, N08.5A
Sjögren's syndrome	734.90	M35.0
Vasculitis syndromes		
Polyarteritis nodosa	446.09	M30.0
Wegener's granulomatosis	446.29	M31.3
Polymyalgia rheumatica and temporal arteritis	446.30, 446.31, 446.39	M31.5, M31.6, M35.3
Vitiligo	709.01	L80, H02.7C
Sarcoidosis	135.99	D86, G53.2, M63.3

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