

Primary Sclerosing Cholangitis: Epidemiological Aspects, Prevalence of elevated IgG4 levels and quality of life

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This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. Lindkvist B, Benito de Valle M, Gullberg B, Björnsson E. Incidence and prevalence of Primary Sclerosing Cholangitis in a defined adult population in Sweden. *Hepatology* 2010; 52 (2): 571-577. (Open access).
- II. Benito de Valle M, Björnsson E, Lindkvist B. Mortality and cancer risk related to Primary Sclerosing Cholangitis in a Swedish population-based cohort. *Liver International* 2011; 32 (3): 441-448. (Open access).
- III. Benito de Valle M, Rahman M, Lindkvist B, Björnsson E, Chapman R, Kalaitzakis E. Factors that reduce health-related quality of life in patients with Primary Sclerosing Cholangitis. *Clin Gastroenterol Hepatol* 2012; 10: 769-775. (Open access).
- IV. Benito de Valle M, Müller T, Björnsson E, Otten M, Volkmann M, Guckelberger O, Wiedenmann B, Sadik R, Schott E, Andersson M, Berg T, Lindkvist B. The impact of elevated serum IgG4 levels in patients with Primary Sclerosing Cholangitis. Manuscript.

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ABSTRACT

Primary Sclerosing Cholangitis: Epidemiological Aspects, Prevalence of Elevated IgG4 Levels, and Quality of Life

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Background and Aims: Primary sclerosing cholangitis (PSC) is a rare cholestatic disease with considerable associated morbidity and mortality. The reported transplant-free survival has ranged between 12-18 years. Epidemiological data and information on health related quality of life (HRQL) in patients with PSC are scarce and mostly provided from referral centers. Liver transplantation (OLT) is the only curative treatment. However, steroid responsiveness has been reported in a subgroup of PSC patients with elevated serum IgG4 values. The aim of this thesis was to investigate the incidence and prevalence of PSC and the risk of malignancy and OLT or death in patients with PSC in a population-based setting in Västra Götaland, Sweden. We also aimed to assess HRQL and the prevalence of elevated serum IgG4 in patients with PSC in the Västra Götaland PSC cohort merged with an English and a German PSC cohort respectively.

Results: The incidence rate of PSC diagnosed during the study period in Västra Götaland Sweden was 1.22 per 100 000 person-years. The incidence of PSC increased by 3% per year (95% confidence interval (CI) 0.01 to 6.20). Thirty-four out of 345 (10%) patients with PSC had elevated serum IgG4 values. A previous history of pancreatitis, intra- and extrahepatic biliary involvement and jaundice were associated with elevated IgG4 in multivariate analysis. Mortality in PSC patients was four times higher (Standardized Mortality Ratio (SMR) 4.20; 95% CI 3.01-5.69) compared with the background population in Västra Götaland. Standardized incidence ratio (SIR) for cholangiocarcinoma (CCA) was 868 (95% CI 505-1390), whereas the SIR for colorectal cancer was not significantly increased compared with the general population. Age, female gender, jaundice, cholangitis and bilirubin were associated with an increased risk of liver-related death or OLT, whereas high age was a risk factor for CCA. Elevated serum IgG4 values was not a risk factor for death or OLT (relative risk (RR) = 0.59, 95% CI (0.28-1.22) or CCA (RR= 0.45, 95% CI (0.06-3.35). Patients with PSC had significantly lower scores from several areas of the short-form 36 (SF-36), compared with controls. Age (β =-0.62 to -0.21, p <0.05) and systemic symptoms (β =3.84-15.94, p <0.05) such as pruritus were associated with lower scores in physical domains, whereas large duct disease with lower scores in vitality domain of the SF-36 (β = -7.10, P <0.05).

Conclusions: The incidence of PSC increased significantly in Västra Götaland during 1992-2005 and the observed prevalence is the highest reported to date. The prevalence of elevated serum IgG4 was similar to that reported in previous studies. The SMR and SIR for hepatobiliary cancer were similar to what has been reported previously in another Swedish study. An unexpected find was that the risk of colorectal cancer was not higher than in the background population. In contrast to previous studies, the prognosis was similar in patients with elevated and normal serum IgG4 values. HRQL was poorer in patients with PSC compared to controls and non life-threatening symptoms such as pruritus were associated with impaired HRQL.

Keywords: Primary sclerosing cholangitis, incidence, mortality, liver transplantation, IgG4, health related quality of life, Västra Götaland, hepatobiliary cancer.