Full analysis of comorbidities in chronic hepatitis C patients compared with matched comparators: a nationwide population-based register study from 2001 to 2013

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BACKGROUND

Patients with chronic hepatitis C (CHC) virus infection have an increased risk of comorbidities (Louie *et al.* 2012). In Sweden, the *International Classification of Diseases*, 10th revision (ICD-10) has been used since 1997 for recording diagnoses in the patient registry (Socialstyrelsen 2018). However, in order to make the analysis of comorbidities easier and more relevant for capturing the extra-hepatic manifestations of CHC, most previous studies have grouped morbidity diagnoses into larger groups, often using comorbidity indexes such as the Charlson comorbidity index or the HepCom (Büsch *et al.* 2017, Ampuero *et al*. 2018). In the present study, we analyzed the risk of comorbidities in patients with CHC patients for all ICD-10 diagnoses.

OBJECTIVE

- Analysis of comorbidities in patients with CHC for ICD-10 diagnoses, both individual diagnoses and in groups of diagnoses.

DISCLOSURES

ML has consultancies with/for AbbVie, BMS, Gilead, Medivir, and MSD/Merck and is a member of the speaker's bureaus for AbbVie, BMS, Gilead, Medivir, and MSD/Merck. MS a founder and board member of Svenska Vaccinfabriken. LF a founder and board member of Svenska Vaccinfabriken. JS, JK, AB, and KB are/were employees of AbbVie and may hold AbbVie stocks or stock options in AbbVie.

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METHODS

SETTING

In Sweden, universal access to health-care is provided to the population through a tax-funded system. Patients with CHC are typically cared for by specialists in infectious diseases or gastroenterology in hospital-based outpatient clinics or inpatient facilities. They are not managed by general practitioners in primary care (Büsch *et al.* 2017).

DATA SOURCES

The National Patient Register (**Table 1**), kept by the Swedish National Board of Health, uses the Swedish adaptation of the ICD-10 called ICD-10-SE (Socialstyrelsen 2018). Patients with CHC were identified using the ICD-10 code B18.2. Data on place of residence, vital statistics, and emigration status were retrieved from the Register of the Total Population held by Statistic Sweden (up to December 31, 2013). This register covers the entire Swedish population and includes information on age, sex, and place of residence, as well as dates of birth, death, and emigration status. Information regarding death was retrieved from the Cause of Death registry. The Swedish personal identity number (social security number) was used to link individuals between registers.

Up to five general population comparators were matched by age, sex, and county of residence to each patient at time of diagnosis/identification.

The study was approved by the Regional Ethics Committee, Karolinska Institutet, Stockholm, Sweden.

STATISTICAL METHODS

Data handling was conducted using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA) and data analyses were performed using Excel (version 14; Microsoft, Seattle, WA, USA). The standardized incidence ratio (SIR) was considered significant if the 95% confidence interval (CI) did not cross 1.

Table 1. Description of the National Patient Register

Register	Description
National Patient Register	Contains all in-patient and non-primary outpatient care visits, such as treatment visits, to an infectious disease specialist or gastroenterologist, but no primary care data. Available register data from: Inpatient care, 1987–2013; Day surgery, 1997–2000; and Non-primary outpatient care, 2001–2013 (including day surgery). It includes information on main and contributory diagnoses based on the *International Classification of Diseases* (ICD-9 1987–1996; ICD-10 1997-2013).

OBSERVATION TIME

The National Patient Register began to include non-primary outpatient care data in 2001; thus, this was used as the starting point in the present study. The observation time began for the CHC cohort at the time of the first physician visit with an accompanying CHC ICD 10-code registration between 2001 and 2013. These index dates were also used for each comparator. The observation time ended at the time of death, emigration, or December 2013, whichever came first.

ASSESSMENTS

The risk was expressed using SIRs with 95% CIs, where the number of observed events was divided by the number of expected events in the CHC cohort based on the events per person-years in the comparator cohort. Since a B18.2 diagnosis was the inclusion criteria for the CHC cohort, the B18.2 diagnosis in the present study was removed when calculating SIRs in both the B18 diagnosis and in the B15-B19 grouped diagnosis.

ABBREVIATIONS

ATC - Anatomical Therapeutic Chemical; **CI** – confidence interval; **CHC** – chronic hepatitis C; **ICD** – *International Classification of Diseases*; MS – multiple sclerosis; **SIR** – standardized incidence ratio

RESULTS

The CHC cohort (n=42,522) was followed for 280,123 person-years (mean 6.59 years) and the comparator cohort (n=202,694) was followed for 1,504,765 person-years (mean 7.42 years). One-third of the patients were men.

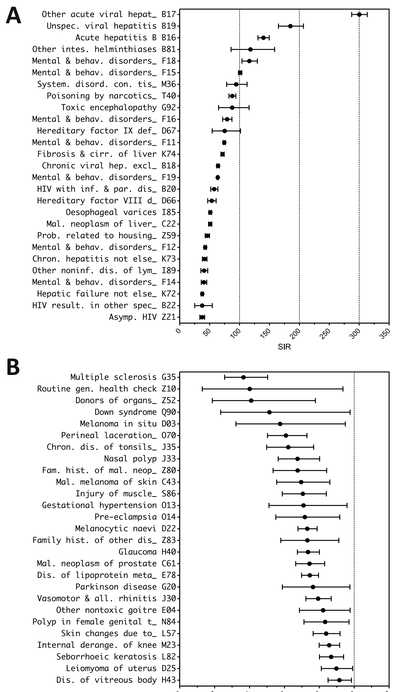
Risk for individual ICD-10 diagnoses

The ICD-10-SE contains 2,213 diagnoses. The lower 95% CI did not cross 1 for 69% of the diagnoses (n=1,122; data not shown), suggesting that patients with CHC to be at an increased risk for these diagnoses. The 27 diagnoses in which patients with CHC were at the highest risk are shown in **Fig. 1A**. The highest risk was "Other acute viral hepatitis" (B17; SIR, 300.2; 95% CI, 287.4-313.5). Patients with CHC are at a lower risk (the upper 95% CI did not cross 1) for 1.2% of the diagnoses (n=27; **Fig. 1B**). The diagnosis with the lowest risk for CHC patients was multiple sclerosis (MS) (G35; SIR, 0.37; 95% CI, 0.26-0.50), which is described in more detail in poster THU-395. It was not possible to calculate the SIR for 31% of the diagnoses (n=694), as either the expected number of patients or the observed number of patients was 0 (most diagnoses were located in ICD-10 chapters XX (V01-Y98), XXI (Z00-Z99), and XXII (U00-U99).

Risk for grouped ICD-10 diagnoses

In total, the ICD-10-SE contains 263 groups of ICD-10 codes. Patients with CHC were at a higher risk for 76% (n=200) and at a lower risk for 1.5% (n=4) of the grouped diagnoses (**Fig. 2**). The highest risk for patients with CHC was "Viral hepatitis" (B15-B19 excluding B18.2; SIR, 86.1; 95% CI, 83.9-88.3) and the lowest risk was for "demyelinating diseases of the central nervous system" (G35-G37; SIR, 0.43; 95% CI, 0.31-0.57). It was not possible to calculate the SIR for 39 diagnoses, as either the expected number of patients or the observed number of patients was 0.

Fig 1. Highest 27 (A) and Lowest 27 (B) Standardized Incidence Ratios (95% CI) for patients with CHC



DISCUSSION

In line with previous studies, patients with CHC were at a higher risk for the majority of diagnoses. The highest risks were seen for other viral hepatitis diagnoses, mental and behavioral disorders, and diagnoses associated with a need for blood products, or diagnoses due CHC sequelae or as a consequence of a more hectic life style.

By analyzing the risk using the by WHO predefined grouped ICD-10 diagnoses, these patients were at a higher risk for all grouped diagnoses within ICD-10 chapters III (blood diseases), IV (metabolic diseases), V (mental disorders), X (respiratory system diseases), XI (digestive system diseases), XIII (diseases of musculoskeletal system and connective tissue), XIV (genitourinary diseases), XVIII (other symptoms), XIX (external injury and poisoning), and XXI (health service contacts).

However, the patients with CHC were at a lower risk for neoplasms in male genital organs (C60-C63), demyelinating diseases of the central nervous system (G35-G37), glaucoma (H40-H42), and radiation-related disorders of the skin and subcutaneous tissue (L55-L59).

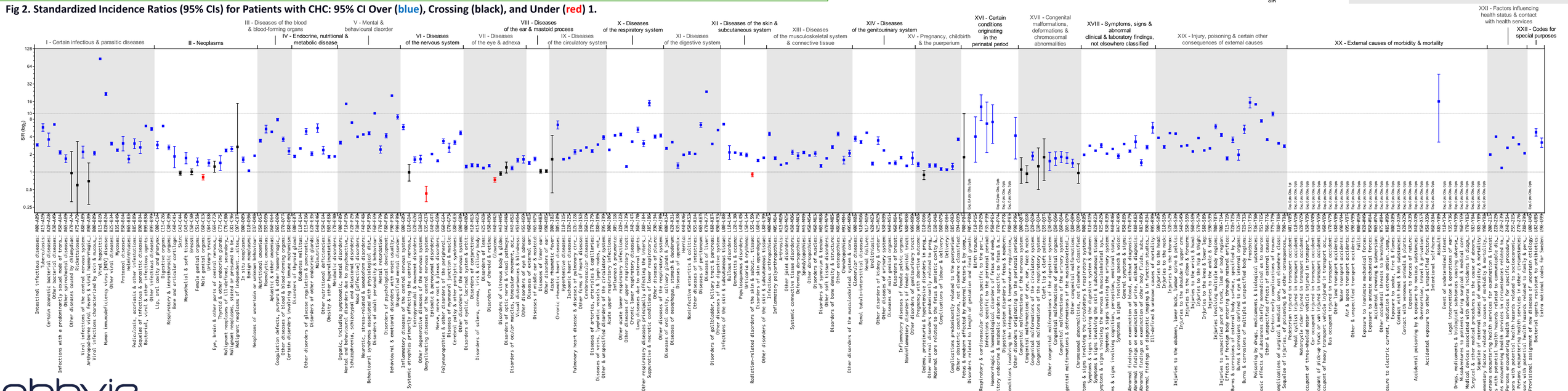
Strengths and limitations

The National Patient Register does not contain any data from visits to a general practitioner, i.e., any diagnoses that mostly received care outside of hospitals could have been underestimated. The study did not included any sensitivity analysis to, for example, avoid surveillance bias due to increased observation of newly diagnosed patients with CHC. Also, the analyses were not adjusted for multiple comparisons.

CONCLUSIONS

- Patients with CHC were at a higher risk for the majority diagnoses. The highest risks were due to riskier behaviors by the patients, mental disorders, disease sequelae, or receiving blood products.
- The patients were at a lower risk for a few diagnoses, such as MS, Down syndrome, glaucoma, prostate neoplasm, and skin changes.

Fig 2. Standardized Incidence Ratios (95% CIs) for Patients with CHC: 95% CI Over (blue), Crossing (black), and Under (red) 1.



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