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.

The design, study conduct, and financial support for the study were provided by AbbVie. AbbVie participated in the study design, data/input analysis, interpretation of results, review, and approval of the publication. The authors determined the final content. No payments were made to the authors for writing this publication

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

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5; ICD

RESULTS

The CHC cohort (n=42,522) was followed for 280,123 personyears (mean 6.59 years) and the comparator cohort (n=202,694) was followed for 1,504,765 person-years (mean 7.42 years). Onethird 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

Other acute viral hepat_ B: viral hepatitis B19 Acute hepatitis B B1 ther intes, helminthiases B disorders F1 ntal & behav. disorders_ F disord. con. tis_ M3 Poisonina by narcotics T4

Toxic encephalopathy GS Mental & behav. disorders_ F Hereditary factor IX def_ D6 Mental & behav. disorders_ F Fibrosis & cirr. of liver K7 Chronic viral hep. excl_ B1 Mental & behav. disorders_ F HIV with inf. & par. dis_ B Hereditary factor VIII d_ D6 Oesophageal varices I

Mal. neoplasm of liver_ C Prob. related to housina_ Z disorders_ Hepatic failure not else_ K7 HIV result. in other spec_ B22-Asymp. HIV Z21

Routine gen. health check Z Donors of organs_ Z Down syndrome Q9 Melanoma in situ D0 Perineal laceration_ 07 Chron. dis. of tonsils_ J3 Nasal polyp J Fam. hist. of mal. neop_ Z80 Mal. melanoma of skin C4 Injury of muscle_ S86 Gestational hypertension 01 Pre-eclampsia 01 Melanocytic naevi D2 Family hist. of other dis_ Z8 Mal. neoplasm of prostate C6 Dis. of lipoprotein meta_ E7 Parkinson disease G2 Vasomotor & all. rhinitis J3 Other nontoxic goitre E0 Polyp in female genital t_ N8

Skin changes due to_ L5 internal derange. of knee M2 Seborrhoeic keratosis L82 Leiomyoma of uterus D25 Dis. of vitreous body H43

XIII - Diseases musculoskeletal system & connective tissue	XIV - Disease of the genitourinary	es system XV - Pregnancy, chilo & the puerperium	XVI - Certain conditions originating Ibirth in the perinatal period	XVII - Congenital malformations, deformations & chromosomal abnormalities	XVIII - Symptoms, signs & abnormal clinical & laboratory findings, not elsewhere classified	XIZ
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·		• . <u>I</u>				• •
		I	Exp. 0.4 pts: Obs. 0 pts Exp. 0.2 pts: Obs. 0 pts Exp. 0 pts: Obs. 0 pts Exp. 0 pts: Obs. 3 pts			
M30-M36- M40-M43- M50-M49- M50-M54- M60-M63- M65-M68- M65-M68- M80-M85- M80-M85- M91-M94- M91-M94-	N60-N69 N10-N16 N10-N16 N17-N19 N20-N23 N20-N23 N30-N23 N40-N21 N60-N51	N70-N77 N80-N98 N99-N99 000-008 010-016 030-029 030-029 030-029 030-029 030-029 030-029 030-029	P00-P04 P05-P04 P10-P15 P20-P29 P35-P29 P50-P24 P75-P78 P80-P83 P90-P96	Q00-Q07 Q10-Q18 Q20-Q28 Q30-Q38 Q38-Q45 Q50-Q56 Q60-Q64 Q65-Q79 Q80-Q89	R00-R09 R10-R19 R20-R29 R20-R29 R20-R29 R40-R46 R40-R46 R40-R49 R50-R99 R83-R89 R83-R89 R80-R94 R95-R99	S00-S09 S10-S19 S20-S29 S30-S39 S40-S49
Systemic connective tissue disorders: Deforming dorsopathies: Spondylopathies: Other dorsopathies: Disorders of synovium & tendon: Other soft tissue disorders: Disorders of bone density & structure: Other osteopathies: Chondropathies:	Other alsorders of the musculoskeletal system & conn_: Glomerular diseases: Renal tubulo-interstitial diseases: Renal failure: Urolithiasis: Other disorders of kidney & ureter: Other diseases of urinary system: Diseases of male genital organs: Disorders of breast:	Inflammatory diseases of female pelvic organs: Noninflammatory disorders of female genital tract: Noninflammatory disorders of genitourinary tract: Dregnancy with abortive outcome: Oedema, proteinuria & hypertensive disorders in preg: Other maternal disorders predominantly related to preg: Maternal care related to the fetus & amniotic cavity &: Complications of labour & delivery: Delivery: Other obstatric conditions, not alsowhere classified.	<pre>Fetus & newborn affected by maternal factors & by comp_: Disorders related to length of gestation and fetal growth: Birth trauma: Respiratory & cardiovascular disorders specific to the peri: Haemorrhagic & haematological disorders of fetus and newb_: Transitory endocrine & metabolic disorders specific to fetus & n: Digestive system disorders of fetus & newborn: Conditions involving the integument & temperature regulation_: Other disorders oriainating in the perinatal period:</pre>	Congenital malformations of the nervous system: Congenital malformations of eye, ear, face & neck: Congenital malformations of the circulatory system: Congenital malformations of the respiratory system: Congenital malformations of the digestive system: Other congenital malformations of the digestive system: Congenital malformations of the urinary system: Congenital malformations of the urinary system: Congenital malformations of the urinary system: Congenital malformations of the musculoskeletal_: Chromosomal abnormalities not elsewhere classified.	<pre>Symptoms & signs involving the circulatory & respiratory systems: Symptoms & signs involving the digestive system & abdomen: Symptoms & signs involving the skin & subcutaneous tissue: Symptoms & signs involving the nervous & musculoskeletal sys. Symptoms & signs involving the urinary system: Symptoms & signs involving the urinary system: Symptoms & signs involving speech & voice: Symptoms & signs involving speech & voice: Abnormal findings on examination of blood, without diagnosis: Abnormal findings on examination of urine, without diagnosis: Abnormal findings on examination of other body fluids, subs. Abnormal findings on diagnostic imaging & in function studies. Abnormal findies on diagnostic imaging & in function studies. Abnormal findies on diagnostic imaging & in function studies.</pre>	Injuries to the head: Injuries to the neck: Injuries to the thorax: Injuries to the thorax: Injuries to the shoulder & upper arm:









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 II (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.

