

Cirrhosis of the liver and diseases of the large joints

PhD dissertation

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Preface

This dissertation is the result of my Ph.D. studies, carried out at the Department of Hepatology and Gastroenterology, and Department of Clinical Epidemiology, Aarhus University Hospital. I would like to thank the people that made this work possible. Foremost, I wish to thank my main supervisor associate professor Peter Jepsen for providing me the privilege to do research under his supervision; for sharing his exceptional skills in clinical epidemiology, biostatistics, and data management; for letting me pursue my own ideas and projects; and for patiently transforming my untidy writings into qualified scientific text. I have learned so much. I also owe my gratitude to Hendrik Vilstrup for contributing with his huge experience and profound insight into hepatology, and for always expecting more from me. As the supervisor team's final member, I would like to thank Søren Overgaard for adding valuable knowledge on clinical and scientific aspects of orthopedic surgery.

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The dissertation is based on the following papers

1. Deleuran T, Vilstrup H, Overgaard S, Jepsen P. Cirrhosis patients have increased risk of complications after total hip or knee arthroplasty. *Acta Orthop* 2014;1-6
2. Deleuran T, Vilstrup H, Overgaard S, Jepsen P. No increased risk for primary osteoarthritis in liver cirrhosis– a Danish population-based cohort study (*submitted*)
3. Deleuran T, Vilstrup H, Overgaard S, Jepsen P. Cirrhosis is a risk factor for avascular necrosis of the hip – a Danish population-based cohort study (*submitted*)

Abbreviations

CCI	Charlson Comorbidity Index
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
DHR	Danish Hip Arthroplasty Register
DKR	Danish Knee Arthroplasty Register
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICD	International Classification of Disease
NPR	National Patient Registry
OR	Odds Ratio
THA	Total Hip Arthroplasty
TKA	Total Knee Arthroplasty

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1 Introduction

This dissertation explores the interplay between cirrhosis and diseases of the large joints.

Study 1 examines cirrhosis patients' risk of complications after total hip or knee arthroplasty (THA/TKA), Study 2 examines cirrhosis as a risk factor for primary osteoarthritis, and Study 3 examines cirrhosis as a risk factor for avascular necrosis of the hip. In the Introduction, cirrhosis is defined, and its impact on the homeostasis is described.

1.1 Cirrhosis

We have previously found that approximately 0.13% of the Danish population have been diagnosed with cirrhosis (1), and cirrhosis is an increasing challenge to public health worldwide (2, 3). It is a severe and life threatening disorder, and Danish cirrhosis patients have a five year survival of only 35% (1, 4, 5). Cirrhosis is the end stage of all chronic liver diseases and alcohol is the most prevalent etiology in Denmark (6). Other etiologies include viral hepatitis, autoimmune hepatitis, genetic, biliary, and metabolic liver disease. These conditions all result in a repeated process of injury and subsequent regeneration with fibrotic tissue. If the injury is not disrupted by treatment (i.e. in viral or autoimmune hepatitis), or by discontinuation of alcohol intake (in alcoholic liver disease) the fibrotic tissue accumulates as regeneration nodules. These nodules are the histopathological hallmark and defining characteristic of cirrhosis, but in clinical practice, the diagnosis is most often based on clinical impression, serum biochemistry, ultrasound, and presence of typical complications. The disturbed liver architecture leads to portal hypertension and loss of liver function.

1.2 The impact of cirrhosis on the homeostasis

The liver has numerous functions including synthesis of serum proteins, metabolism of nutrients and drugs, and protection of the systemic circulation from the gut microbiota, and it constitutes an important element of the reticuloendothelial system. The importance of these functions is highlighted by the profound disturbance of the circulation, the electrolyte balance, and the immune system imposed by cirrhosis (7-9). The best described

consequences of these disturbances are the ‘classical’ cirrhosis complications: variceal bleeding, ascites, hepatic encephalopathy, hepatorenal syndrome, and spontaneous bacterial peritonitis (SBP). However, cirrhosis has also been associated with other conditions: venous thromboembolism, infections other than SBP, cancer, and autoimmune disease (10-13). Thus, it is increasingly recognized that the clinical entity ‘cirrhosis’ is a systemic disease, rather than a one-organ dysfunction (14). This dissertation examines two lesser-known aspects of cirrhosis’ pathophysiology that emphasize the systemic nature of cirrhosis: cirrhosis patients’ impaired ability to tolerate surgery and the consequences of their chronic systemic inflammation.

1.2.1 Surgery on cirrhosis patients

Cirrhosis patients’ high risk of complications after surgery has been known for decades. The widely used Child-Pugh score that is used to stage cirrhosis severity was originally developed to predict cirrhosis patients’ risk of complications after surgery (15).

The causes of cirrhosis patients’ increased risk of complications after surgery are unknown, but several reasons have been proposed (16, 17):

- Intolerance to anesthetic agents because of altered binding to plasma proteins, detoxification, and excretion
- Susceptibility to bacterial infections
- Increased size and frailty of veins in the hepatic portal system
- Coagulation defects

Cirrhosis patients’ risk of complications after intra-abdominal surgery has been studied for many procedures and in many settings (17-21). The 30-day mortality is 7% after open cholecystectomy and 8% after appendectomy (22, 23). The high absolute risks of complications in intra-abdominal surgery have been attributed to cirrhosis patients’ portal hypertension. Knowledge on *absolute* risks of surgical complications is important because it guides clinicians’ and patients’ decision. However, knowledge of *relative* risks of complications for patients with vs. without cirrhosis is also important; it can teach us about

the extent of the systemic disturbance of cirrhosis, because relative risks estimates enable confounder adjustment. Cirrhosis patients' risk of complications after extra-abdominal surgery is less well-described, even though the relative risk of complications in this context is of particular interest. The increased risk imposed by the frailty and size of veins in cirrhosis patients' hepatic portal system is absent in extra-abdominal surgery. Consequently, there is reason to assume that extra-abdominal surgery in cirrhosis patients is less unsafe than intra-abdominal surgery. So, the causes of cirrhosis patients' inability to tolerate surgery can be further clarified by comparing cirrhosis patients' risk of complications after extra-abdominal surgery with this risk in patients without cirrhosis.

1.2.2 Chronic systemic inflammation

The term inflammation was originally coined by Celsus and describes four clinical signs: *calor, dolor, tumor, et rubor*. With progresses in cell biology and molecular biology this term has evolved to describe mechanisms rather than signs and symptoms (24, 25). Two of the signs of inflammation — *calor* and *rubor* are ascribed to inflammatory processes' ability to induce vasodilation, and cirrhosis patients' hyperdynamic and vasodilated systemic circulation is caused by pro-inflammatory cytokines (14, 26-28). Albillos et al. have summarized the evidence for cirrhosis patients' chronic systemic inflammation (26). This evidence includes increased expression of surface antigens that activate circulating immune cells (neutrophils, T-cells); increased production and serum levels of pro-inflammatory cytokines (e.g. Tumor Necrosis Factor- α , Interferon- γ , Interleukin-1 β , Interleukin-6); increased serum level of acute phase reactants and endothelial activators (C-Reactive Protein and Intercellular Adhesion Molecule-1). Thus, cirrhosis patients have chronic systemic inflammation and it is evident from their clinical presentation. However, the consequences of cirrhosis patients' chronic systemic inflammation are unclear, but inflammation has been proposed as a risk factor for several conditions, including disease of the musculoskeletal system.

Thus, cirrhosis is a systemic disease whose pathophysiology impairs the ability to tolerate surgery and causes chronic systemic inflammation. However, the significance of these disturbances for diseases in the large joints is unknown.

2 Background

2.1 Total hip or knee arthroplasty

Total joint arthroplasty is a surgical procedure with which the surface of a dysfunctional joint is replaced by a prosthetic implant. It is used as a treatment for dysfunction of the hip, knee, shoulder, ankle, elbow, and wrist, and the most common procedures are total hip and knee arthroplasty. This dissertation will focus on these two procedures for which primary osteoarthritis is the most common indication (29, 30). Total hip or knee arthroplasty is increasingly common and is considered a safe and well-tolerated treatment (31-33). Although a recent Danish randomized controlled trial questions whether arthroplasty is superior to conservative treatment for knee osteoarthritis in the general population (34). Total hip or knee arthroplasty offers a unique opportunity to study how cirrhosis affects the outcome after extra-abdominal surgery.

2.1.1 Existing literature

I searched for studies on cirrhosis patients' risk of complications after total hip or knee arthroplasty using this Medline query:

("Liver Cirrhosis"[Mesh] AND "Risk"[Mesh]) AND ("Arthroplasty,
Replacement, Hip"[Mesh] OR "Arthroplasty, Replacement, Knee"[Mesh])

This search produced 8 results. After reviewing the abstracts of these publications, 6 were relevant (35-40). Due to the small number of hits the query was expanded to:

("Liver Cirrhosis"[Mesh]) AND ("Arthroplasty, Replacement, Hip"[Mesh]
OR "Arthroplasty, Replacement, Knee"[Mesh])

This search only produced 5 additional hits, but none of them involved risk estimation for cirrhosis after total hip or knee arthroplasty. Then I expanded the search further:

("Arthroplasty"[Mesh]) AND "Liver Cirrhosis"[Mesh]

This search produced two additional hits, but none of them were relevant. Similar queries were made in Scopus and Embase and yielded one additional reference (41). However, only the abstract could be reviewed, since the publication was in Chinese. The reference lists of these relevant 7 publications (Table 1) were reviewed, but they identified no additional references. Further, the Scopus database was searched for publications that cited one or more of these 7 studies or Study 1, but this search produced no more relevant results. Of note, the papers by Tiberi II et al. and Jiang et al. were published after we submitted Study 1 (39, 40).

Table 1: Studies on cirrhosis patients' risk of complications after hip or knee arthroplasty, OA: osteoarthritis, AVN: avascular necrosis.

Publication (Country)	Cirrhosis patients (arthro- plasties)	Reference patients	Setting	Child- Pugh	Surgical procedure (N)	Indication	30-day risk of mortality / complications in cirrhosis patients	Odds ratio for mortality/ complications for cirrhosis patients vs. reference patients
Hsieh 2003 (Taiwan)	38 (45)	No	1 hospital	A: 62 % B: 31 % C: 7 %	THA	AVN (60%) Fracture (18%) Infection (11%) Primary OA (11%)	0 / 26 .7%	-
Shih 2004 (Taiwan)	51 (60)	42 (51)	1 hospital	A: 98 % B: 2 %	TKA	Primary OA	4.8% / unclear %	- / 12.1
Cohen 2005 (United States)	25 (29)	89 (93)	1 hospital	-	Elective THA (14) Acute THA (5) Elektiv TKA (10)	Primary OA (92%) Fracture (8%)	10.3 % / 41.3%	10.6 / 2.7
Moon 2007 (South Korea)	30	No	1 hospital	A: 63 % B: 30 % C: 7 %	Elective THA (17) THA revision (5) Hemi-HA (8)	AVN (52%) Fracture (40%) Primary OA (8%)	6.7 / 27 %	-
Xu 2013 (China)	13	No	1 hospital	A: 7 B: 6	THA (13)	Unclear	0 / 30.7%	-
Jiang 2013 (United States)	2,109	878,677	Multiple hospitals	-	THA (878) TKA (1,231)	Fracture/Non- fracture (see text)	1.0 % /See footnote*	See footnote*
Tiberi III 2014 (United States)	115	115	1 hospital	-	THA (60) TKA (55)	Primary OA (100%)	1% / 62%	-/7.6 (medial compl.), 10.5 (surgical compl.)

*1 year risk of perioperative infection after THA: 3.7%, after TKA: 2.7%. HR for readmission after THA: 2.2, after TKA: 1.8. Overall inhospital mortality risk: 1%. Mortality HR after THA: 9.8, after TKA: 3.6.

Table 1 shows the characteristics and results of studies on cirrhosis patients' risk of complications after total hip or knee arthroplasty (35-40). Most of the risk estimates and odds ratios (ORs) in this table were based on numbers extracted from tables in the papers and computed by me.¹

There is evidence that the indication for total hip or knee arthroplasty affects the outcome (29). Hsieh et al. found that 38% of total hip or knee arthroplasties' needed revision in their cohort, and avascular necrosis was the predominant etiology in this study (35). Based on the findings of Cohen et al., I computed a mortality OR of 10.6 for cirrhosis vs. reference patients, but all the deaths occurred after total hip arthroplasty for fracture (38) (Table 1). Moreover, Jiang et al. found the impact of cirrhosis on mortality in hip arthroplasty (HR=9.8) to be twice as high as in knee arthroplasty (HR=3.6). The most likely explanation to this difference is that the cohort which underwent hip arthroplasty included patients with fractures, whereas patients with fractures were absent in the cohort which underwent knee arthroplasty (39).

The definition of complications varied across the studies. Most of the studies recorded both surgical and medical complications, but none of provided separate estimates for each type. However, several studies reported that infection or renal failure were particularly frequent in cirrhosis patients (37, 38, 40). Also the period in which complications were registered varied from 30 days (37, 38), to the entire follow-up period (36). Four studies provided the opportunity to estimate the impact of cirrhosis on the risk of complications (36, 38-40), and two of them— Shih et al. and Tiberi II et al. — studied patients that underwent total hip or knee arthroplasty for primary osteoarthritis. Based on their findings, I found an OR for complications between 8 and 10 (Table 1). However, the interpretation of these results were impeded the varying definitions of complications. Thus, the existing evidence of cirrhosis' impact on the risk of complications after total hip or knee arthroplasty indicates that cirrhosis patients are at an increased risk, and that infections and renal failure were particularly frequent (37, 38, 40).

¹ OR= $\frac{N \text{ with outcome in exposed} / N \text{ without outcome in exposed}}{N \text{ with outcome in unexposed} / N \text{ without outcome in unexposed}}$, OR for death in Cohen et al. = $\frac{3/26}{1/92} = 10.6$

As shown in Table 1, the cirrhosis patients' absolute mortality ranged from 0% - 10%. The variation in mortality was probably due to differences in the indication for arthroplasty and the small study size, but most of the studies reported cirrhosis patients' risk of complication to be over 30%. Of note, Jiang et al. found a periprosthetic infection risk at 6 months of about 3% for cirrhosis patients vs. 0.7–0.8% in patients without cirrhosis (Table 1). As a final point, several of the studies reported that the risk of mortality and complications increased with the severity of liver disease (35-38, 40).

2.1.2 The ideal study

The aim of Study 1 was to clarify whether cirrhosis patients had an increased risk of complications after orthopedic surgery and to clarify its causes. The ideal way to settle these uncertainties is to perform an experiment where a patient cohort is randomized to have either 'cirrhosis' or 'no cirrhosis' and subsequently undergoes exactly the same orthopedic procedure. Obviously, this experiment remains impossible. The realistic alternative is to design an observational study in which the patients are as similar as possible, except for the presence or absence of cirrhosis, and undergo the same orthopedic procedure. This similarity could be maximized by studying cirrhosis and reference patients that undergo total hip or knee arthroplasty for the same indication, and by choosing an indication for which the procedure is an option rather than a necessity. Cirrhosis patients operated for such an indication most likely have compensated cirrhosis (i.e. have no complications such as variceal bleeding, ascites, etc.). In this manner, it is clarified whether or not the least 'sick' cirrhosis patients also are at an increased risk of complications after orthopedic surgery. Another important step is to exercise thorough confounder control.

2.1.3 Limitation of existing literature

The purpose of the literature review was to clarify whether such a study had been performed before. As shown in Table 1 (page 7) several studies have examined cirrhosis patients' risk of

complications after total hip or knee arthroplasty, but none of them aimed to approximate the criteria for the ‘ideal’ study on cirrhosis impact on surgery outlined above:

- Most of the studies included patients treated for a range of different indications: primary osteoarthritis, avascular necrosis of the hip, fracture, deep prosthesis infections, or unknown indication (35-40).
- Some of the studies included both acute and elective procedures.
- The definition of complications varied across the studies.
- The period in which complications were registered varied from 30 days (37, 38), to the entire follow-up period (10.6 years) (36).
- Most of these previous studies were small and based on single center experiences (35-40).
- The only study that was based on the experience from multiple centers was published after we submitted paper 1 (39). The only information about the indication for arthroplasty in this study was whether or not it was a fracture.

Thus, to close the gap in the existing literature on the risk of complications after total hip or knee arthroplasty in cirrhosis patients, and to ensure that it had the broadest possible generalizability, a *population-based* cohort study was conducted (42). To ensure the most homogeneous study population, the study was restricted to cirrhosis patients that underwent total hip or knee arthroplasty for primary osteoarthritis. Finally, it was important to settle whether general anesthesia was a cause of complications in surgery on cirrhosis patients. In this manner, only immune deficiency and coagulation defects remained as plausible causes to cirrhosis patients’ increased risk of complications after surgery (as outlined on page 2).

2.2 Primary osteoarthritis

Primary osteoarthritis is caused by breakdown of cartilage and underlying bone without any previous dysfunction or injury of the affected joint. The main symptoms are pain and stiffness leading to loss of function and low health-related quality of life (43). The diagnosis

relies on a combination of symptoms, clinical examination, and radiological evidence. Primary osteoarthritis is one of the most prevalent chronic diseases in the Western World (44, 45), and approximately 30% of persons over 60 years have radiological evidence of primary osteoarthritis (45). The pathogenesis has been considered as an inevitable part of aging in combination with mechanical stress (46). However, it is increasingly recognized as a multifactorial disease caused by a combination of metabolic, genetic, and mechanical factors; in this context inflammation is considered a key component (47). Indeed, several studies have linked elevated serum markers for inflammation to symptoms in primary osteoarthritis (48, 49). Nevertheless, the involvement of inflammation in the pathogenesis of primary osteoarthritis remains unresolved (50).

2.2.1 Cirrhosis patients' risk of primary osteoarthritis

Cirrhosis patients offer a unique opportunity to study chronic systemic inflammation as a risk factor for primary osteoarthritis (26). Such knowledge is important because any attempt to prevent a disease requires knowledge about its causes. In addition, the main treatment for severe osteoarthritis is total joint replacement, and this treatment is associated with a high risk of complications in cirrhosis patients—the subject of Study 1 (51, 52).

2.2.2 Existing literature

I searched for studies on cirrhosis patients' risk of primary osteoarthritis using the Medline query:

"Liver Cirrhosis"[Mesh] AND ("Osteoarthritis"[Mesh] OR "Osteoarthritis, Knee"[Mesh] OR "Osteoarthritis, Hip"[Mesh])

This search produced 23 hits including Study 1 (51). These studies concerned a variety of topics, e.g. stroke, pharmacokinetics of etodolac, or hemochromatosis, but none of them

involved studies on cirrhosis patients' risk or incidence rate of primary osteoarthritis. Similar queries were made in Embase and Scopus, but neither of these searches produced any relevant results.

2.2.3 Limitation of existing literature

Cirrhosis patients' risk of primary osteoarthritis is unknown, but as argued above (paragraph 2.2.1), it is important to clarify the impact of chronic systemic inflammation on the risk of primary osteoarthritis. In this context, cirrhosis patients' incidence rate of primary osteoarthritis was compared with the incidence rate of age-, gender-, and birth date-matched persons without cirrhosis from the general Danish population in a nationwide historical cohort study.

2.3 Avascular necrosis of the hip

Avascular necrosis is necrosis of bone cells. It occurs in bone parts with frail circulation such as the femoral head, in the femur part of the knee distal to the epiphyseal line, and in carpal bones. Only avascular necrosis of the hip was considered in this dissertation.

Avascular necrosis of the hip is a rare condition that causes instability leading to collapse of the femoral head. Insufficient blood supply is the precipitating event, and in some cases it has an obvious cause: trauma, surgery, or radiation (53). In other cases the cause is less obvious, but a number of risk factors have been identified: corticosteroid treatment (54), alcohol intake, and smoking (55, 56). Various conditions including coagulopathy, gout, hematological disease (57), organ transplantation (58), and HIV (Human Immunodeficiency Virus) infection (59) also increase the risk of avascular necrosis. Despite the awareness of these risk factors, it is unclear how they cause avascular necrosis of the hip, and knowledge on other risk factors may help to clarify the pathogenesis.

2.3.1 Cirrhosis patients' risk of avascular necrosis

One previous study has identified cirrhosis as a risk factor for avascular necrosis in a Korean cohort of hospital patients (60). Cirrhosis patients have an increased risk of thromboembolic events (10), cancer (12), infections (61), and autoimmune disease (13), but it is unclear whether cirrhosis patients are susceptible to joint disease. Avascular necrosis of the hip has been linked with inflammation (62), endothelial dysfunction (63), and coagulopathy (64), which are essential features of cirrhosis pathophysiology (10, 26, 65). Thus, cirrhosis is likely to be a risk factor for avascular necrosis. Such knowledge is clinically relevant since many patients with avascular necrosis undergo total hip arthroplasty. Avascular necrosis is a risk factor for a poor outcome after this procedure and — as Study 1 showed — also cirrhosis is a risk factor for a poor outcome after total hip or knee arthroplasty (51, 52).

2.3.2 Existing literature

I searched for studies on cirrhosis patients' risk of avascular necrosis using the Medline query:

(("Osteonecrosis"[Mesh]) AND "Liver Cirrhosis"[Mesh]) AND "Risk"[Mesh]

This search identified 4 studies. Only one of them was on cirrhosis patients' risk of avascular necrosis of the hip (60). Of the remaining studies, two were studies of pain, fracture, and avascular necrosis of the hip after liver transplantation for cholestasis (66, 67), and the third was a study of avascular necrosis of the hip after liver transplantation for hepatitis B and HIV co-infection (68). Similar queries were performed in Embase and Scopus, but these queries did not expand the number of relevant studies. In parallel with the search strategy employed in section 2.2.1 (page 6), the reference list of the only relevant study were reviewed and the Scopus database was used to retrieve publications that cited it. This additional search produced no additional studies.

2.3.3 Limitation of existing literature

Current knowledge on cirrhosis as a risk factor for avascular necrosis rests on just one study (60). This study examined cirrhosis patients' risk of avascular necrosis of the hip with data from the Taiwan National Health Insurance research database. It compared cirrhosis patients' and other hospitalized patients' risk of avascular necrosis of the hip. In this study, the adjusted hazard ratio for avascular necrosis of the hip for cirrhosis patients vs. non-cirrhotic patients was 2.38 (95% CI: 1.89–2.99). This study had certain limitations: It examined the risk of avascular necrosis of the hip in cirrhosis patients vs. other hospitalized patients, and even though this hazard ratio was adjusted for certain comorbidities that predispose to avascular necrosis of the hip, only conditions recorded at the current hospital admission were considered. Further, this design implies that cirrhosis patients' risk of avascular necrosis was compared to the risk in patients with "other disease", which makes the hazard ratio difficult to interpret. Finally, the findings were not supported by evidence of their data sources' validity.

So, it is important to verify the findings of Hung et al. in a different population with validated data sources and to assess the actual impact of cirrhosis on the risk of avascular necrosis. Therefore, a registry based cohort study was conducted comparing the incidence rate of avascular necrosis of the hip in cirrhosis patients and age- and gender matched reference persons from the general Danish population.

3. Aims

The aim of this dissertation was to study selected aspects of cirrhosis' interplay with joint disease. Specifically, the aim was to answer the following questions:

- Are cirrhosis patients at an increased risk of complications including mortality after total hip or knee arthroplasty compared with patients without cirrhosis that undergo the same procedyre? Such knowledge will:
 1. Provide insight into the systemic disturbance imposed by cirrhosis.
 2. Guide patients and clinicians about the risks associated with total hip or knee arthroplasty in cirrhosis patients.
- Is cirrhosis a risk factor for primary osteoarthritis? Such knowledge may:
 1. Clarify whether chronic systemic inflammation is a risk factor for primary osteoarthritis.
 2. Have clinical implications, since cirrhosis is a risk factor for complications after total hip or knee arthroplasty.
- Is cirrhosis a risk factor for avascular necrosis of the hip? Such knowledge will
 1. Help clarify the pathophysiology of avascular necrosis of the hip.
 2. Provide clinical insights, since cirrhosis is a risk factor for complications after total hip or knee arthroplasty.

4. Methods

4.1 Setting

All three studies were nationwide Danish cohort studies. Danish residents have access to the tax funded Danish healthcare system, which ensures equal access to treatment in primary and secondary healthcare facilities.

4.2 Data sources

All three studies were based on data from the following sources:

4.2.1 The Danish Civil Registration System

The Danish Civil Registration System was founded in 1968 and contains complete and continuously updated information on the residence, vital status and date of death of all Danish residents. It issues a unique 10-digit personal identifier at birth or immigration which enables linkage of individual-level information between Danish medical and administrative registries. In addition, the personal identifier describes the birth date and the gender of the holder (69, 70).

4.2.2 The National Patient Registry

The Danish National Patient Registry (NPR) is a nationwide registry that holds data on non-psychiatric in-hospital admission and surgical procedures in Denmark since 1977. Each contact is described by one primary and up to 20 secondary diagnoses coded in accordance with the International Classification of Disease edition 8 (ICD-8) until 1994, and the ICD-10 thereafter. The diagnoses are assigned at discharge by the physician who discharges the patient. From 1995, the NPR also includes data from outpatient and emergency room visits. All hospital contacts are described by one or two dates. In-patient hospitalizations are described by the admission- and discharge date, emergency room visits are described by the visit date, and outpatient visits are described by the first and the last visit date (71).

4.2.3 The Danish Hip and Knee Arthroplasty Registries

The Danish Hip Arthroplasty Registry (DHR) and the Danish Knee Arthroplasty Registry (DKR) are clinical databases that contain data on all primary and revision arthroplasties performed in Denmark since 1995 (DHR) and 1997 (DKR). Using procedures registered in the NPR as the gold standard, the completeness of the DHR and DKR are 94% and 88%, respectively (30, 72). The data is provided by the operating surgeon and includes the indication for the procedure (primary osteoarthritis, avascular necrosis of the femoral head, or other indication), type of anesthesia (local/general), data on intraoperative complications, and revisions (30, 72).

4.3 Study design

Cirrhosis was the exposure in all three studies. It was defined as a hospital contact in the NPR that resulted in a diagnosis for either alcoholic cirrhosis (ICD-8: 571.09; ICD-10: K70.3, K70.4) or unspecified cirrhosis (ICD-8: 571.92, 571.99; ICD-10: K74.6).

4.3.1 Study 1

Study 1 was a historical cohort study. All Danish residents who underwent total hip or knee arthroplasty for primary osteoarthritis according to the DHR/DKR from January 1 1995 to December 31 2011 were identified, and only their first hip or knee arthroplasty was considered. Patients with a diagnosis for cirrhosis before the total hip or knee arthroplasty constituted the cirrhosis patients. The remaining were reference patients.

To identify a marker for cirrhosis severity in Study 1, cirrhosis patients were further subdivided into those with portal hypertension, defined by a diagnosis for bleeding esophagus varices (ICD-8: 456.01, 456.09; ICD: I85.0), gastric varices (ICD-10: I86.4), or portal hypertension (K76.6) before the total hip or knee arthroplasty, and those without portal hypertension.

4.3.1.1 Confounders Study 1

The risk of complications was compared for cirrhosis patients vs. reference patients with adjustment for differences in age, gender, level of comorbidity. In Study 1, comorbidity was defined according to the Charlson Comorbidity Index (CCI) modified for usage with ICD-10 codes (73, 74). It is a weighted comorbidity score including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer, mild liver disease, diabetes with or without complications, hemiplegia or paraplegia, renal disease, cancer, moderate or severe liver disease, metastatic cancer, and HIV/AIDS. Liver disease was not a comorbidity in Study 1 and was therefore excluded from the Charlson Comorbidity Index.

Apart from age, gender, and comorbidity, several other factors could potentially be associated with both cirrhosis (the exposure) and the outcome (mortality and complications). To reduce residual confounding from comorbidity, NPR data was used to compute the number of in-hospital admissions in the year before the arthroplasty. Moreover, the estimates were adjusted for procedural characteristics identified in the DKR/DHR: operation site (hip/knee), type of anesthesia (general/regional), and year of operation.

4.3.1.1 Outcomes Study 1

The outcomes were death and complications during the admission for the arthroplasty procedure or within 30 days after discharge. Complications included intraoperative complications (fissure or fracture of the acetabulum, femur, or tibia), transfer to an intensive care unit or a medical department, or readmission within 30 days after discharge.

Readmissions were further categorized as being due to infections, liver disease, acute renal failure, venous thromboembolism, cardiovascular disease, hip dislocation or mechanical complications, or other diagnoses. For hip dislocations, emergency room visits were also considered.

The function of the prosthesis is relevant beyond the first 30 days post discharge, so follow-up for periprosthetic infection (ICD-10 diagnosis in the NPR: T84.5, T84.6, T84.7) or revision arthroplasty (according to the DHR/DKR), or death continued for a full year after the arthroplasty.

4.3.2 Study 2

Study 2 was a matched historical cohort study. Primary osteoarthritis affects the elderly (46), so diagnoses for primary osteoarthritis in persons younger than 60 year may reflect other conditions. Therefore, all Danish residents who had a first time diagnosis for cirrhosis in 1994–2011 when they were 60 years or older, were identified. The “index date” was defined as the date of the first diagnosis for cirrhosis. Patients who before the index date had a diagnosis for osteoarthritis or for a cause of secondary osteoarthritis (Table 2), or underwent total hip or knee arthroplasty were excluded. The remaining cirrhosis patients were matched 1:5 on age, gender and birth date to a cohort of reference persons from the general Danish population using risk set sampling (75). Reference persons were excluded according to the same criteria as cirrhosis patients and were assigned the same index date as their corresponding cirrhosis patient. The exclusion of reference persons with causes of secondary osteoarthritis had the effect that not all cirrhosis patients were matched 1:5.

Table 2: Causes of secondary osteoarthritis of the hip or knee

Disorder	ICD-8	ICD-10
Avascular necrosis		M87.0
Calve-Legg-Perthes	722.11	M91.1
Congenital hip dislocation	755.69	Q65.x
Epifysiolyis	722.10	M93.0
Fracture of distal femur, patella, or proximal tibia	821.xx, 822.xx, N823.xx	S82.0, S82.1
Hip fracture, acetabulum fracture	820.xx	S32.4, S32.5, S72.x
Hip dislocation, knee dislocation	835.xx, 836.xx	S73.x, S83.x
Rheumatoid arthritis, other arthritis	710.xx, 711.xx, 712.xx, 714.xxx, 715.xx	M0x.x, M10.x, M11.x, M12.x, M13.x, M14.x

Since smoking may be protective for primary osteoarthritis (76), the NPR was used to identify emergency room visits, in- and outpatient contacts for chronic obstructive pulmonary disease (COPD) before the index date, as an indicator for smoking.

The primary outcome was time to a diagnosis for primary osteoarthritis of the hip or knee in the NPR (ICD-10: M16.0, M16.1, M17.0, or M17.1). Cirrhosis patients and reference persons were followed from the index date to the first diagnosis for primary osteoarthritis, death, or end of follow up on December 31 2011. The secondary outcome was defined as time to a diagnosis for primary osteoarthritis of the hip or knee (as defined above) *and* a subsequent arthroplasty for primary osteoarthritis according to the DHR/DKR *at the same site*. When this composite outcome was examined, follow-up was until the arthroplasty for primary osteoarthritis.

4.3.3 Study 3

Study 3 was a matched historical cohort study. Cirrhosis patients who had a first time diagnosis for cirrhosis in 1994–2011 were identified. The index date was defined according to the same criteria as Study 2 (page 20). All cirrhosis patients that before the index date underwent total hip arthroplasty, were diagnosed with avascular necrosis (M87.0), or had a diagnosis for a hip fracture (ICD-8: 820.xx, 821.xx; ICD-10: S72.0) were excluded. The remaining cirrhosis patients were matched to reference patients. The reference persons were matched in the same way as in Study 2 (page 20) and excluded according to the same criteria as the cirrhosis patients.

To address potential confounders in Study 3, the NPR was used to identify hospital contacts for conditions predisposing to avascular necrosis of the hip, and to identify indicators for smoking, corticosteroid treatment (Table 3), and alcoholic etiology to cirrhosis (Table 4).

Table 3: Conditions predisposing to avascular necrosis, and indicators for smoking and for corticosteroid treatment with ICD-8 and ICD-10 codes

	ICD-8	ICD-10
Conditions predisposing to AVN:		
Human Immunodeficiency Virus	079.83	B20.x–B24.x
Myeloproliferative disease	20x.x	C88.x, C90.x–C96.x
Hemoglobinopathy	282.x	D55.x– D59.x
Diabetes mellitus	249.x, 250.x	E10.x–E14.x
Gout	274.0	M10.x
Chronic renal failure	58x.x	N18.x
Solid organ transplantation	Y95.x	Z94.x
Indicator for smoking:		
Chronic obstructive lung disease	490.x–492.x	J43.x–J44.x
Indicators for corticosteroid treatment:		
Autoimmune hepatitis	573.02	K73.2, K75.4
Rheumatoid arthritis	712.0x–712.2x	M05.x
Connective tissue disease	734.x	M3x.x

Table 4: Indicators for alcoholic etiology to cirrhosis with ICD-8 and ICD-10 codes

	ICD-8	ICD-10
Alcohol induced pseudo-Cushing's syndrome		D24.4
Mental and behavioral disorders due to use of alcohol	291.xx,303.xx	F10.x
Degeneration of nervous system due to alcohol		G31.2
Alcoholic polyneuropathy		G62.1
Alcoholic myopathy		G72.1
Alcoholic cardiomyopathy		I42.6
Alcoholic gastritis		K29.2
Alcoholic hepatitis		K70.1
Alcoholic fatty liver and unspecified alcoholic liver disease		K70.0, K70.9
Acute alcoholic pancreatitis		K85.2
Chronic alcoholic pancreatitis		K86.0
Ethanol poisoning		T51.0

The outcome in Study 3 was time to a hip arthroplasty for avascular necrosis. Cirrhosis patients and reference persons were followed from the index date to the date of the hip arthroplasty for avascular necrosis, death, or end of follow-up on December 31 2011.

4.4. Statistical analysis

4.4.1 Study 1

The crude 30-day risk of mortality and complications was computed as:

$$\frac{\text{number of patients with outcome}}{\text{number of patients included}}$$

Ideally, the absolute risks of mortality and complications in cirrhosis and reference patients should be compared in a relative risk, but it is difficult to compute with the Mantel-Haenszel method when more than one confounder is included, because this method relies on data stratification. Consequently, the adjusted odds ratio (aOR) for mortality and complications for cirrhosis patients vs. reference patients was estimated using logistic regression. In studies with rare outcomes—an absolute risk below 5% in the unexposed as a rule of thumb—the odds ratio resembles the relative risk (77). So, the odds ratios presented in Study 1 can be interpreted as relative risks. These estimates answer the etiological question: “Is cirrhosis a risk factor for complications after total hip or knee arthroplasty?”

To assess whether the risk of complications increased with the severity of liver disease, the mortality was compared for cirrhosis patients with and without portal hypertension (as defined on page 18). Moreover, to examine whether even the most well-compensated cirrhosis patients remained at a higher risk of complications than reference patients, the regression analysis was repeated twice. First, it was *restricted* to cirrhosis patients without portal hypertension compared with reference patients. Second, it was *restricted* to cirrhosis and reference patients operated in regional anesthesia. Finally, the probability of an uncomplicated hip or knee arthroplasty (the proportion of patients without complications) was computed for cirrhosis patients and reference patients.

The cumulative incidence function accounting for death as competing risk was used to compute the 1-year risk of periprosthetic infection and revision arthroplasty in patients with and without cirrhosis. This estimate answers the clinical question: “What proportion of

patients will have a periprosthetic infection / revision arthroplasty within one year after hip or knee arthroplasty?” The subdistribution hazard ratio was estimated in order to examine whether cirrhosis increased these 1-year risks after confounder adjustment (78).

4.4.2 Studies 2 and 3

The crude incidence rate of primary osteoarthritis (Study 1) and avascular necrosis (Study 2) was computed for cirrhosis patients and for reference persons as:

$$\frac{\text{number of persons diagnosed with primary osteoarthritis}}{\text{total follow-up time}}$$

Stratified Cox regression was used to estimate the hazard ratio (HR) for primary osteoarthritis and avascular necrosis of the hip for cirrhosis patients vs. reference persons adjusted for confounders. Stratified Cox regression is the standard analysis in matched data (79). The HR can be interpreted as the incidence rate ratio and answers the etiological question: “Is cirrhosis a risk factor for primary osteoarthritis/avascular necrosis.”

In Study 2, the crude incidence rate was computed stratified by age group. The HR (or incidence rate ratio) was estimated for cirrhosis patients vs. reference persons within strata defined by age and gender. The purpose of these stratified analyses was to identify *effect measure modification* i.e. whether the effect of the exposure (cirrhosis) varied across subgroups. The HR was also computed by site (hip/knee) to examine whether cirrhosis had a distinctive effect in each joint. Finally, to verify our findings, the HR for the composite outcome (diagnosis + arthroplasty) was computed.

In Study 3, alcohol intake may confound the association between cirrhosis and avascular necrosis of the hip. However, alcoholic cirrhosis patients are expected to drink more alcohol than reference patients who drink alcohol. Therefore, it was most relevant to examine the association in cirrhosis patients and reference persons without alcohol intake. So, an additional regression analysis was made *restricted* to patients with unspecified cirrhosis (i.e. *without* alcoholic cirrhosis) and without a previous hospitalization for an alcohol related disorder (Table 4, page 22). Accordingly, reference persons who previously were hospitalized

for an alcohol-related disorder were also excluded from this analysis. This analysis will not eliminate confounding from alcohol, but it increases the likelihood of causal relation if the association is preserved.

In study 3, the 1-year risk of avascular necrosis was computed using the cumulative incidence function with death as competing risk. This analysis answers a clinical question (“what proportion of cirrhosis patients will have avascular necrosis?”) rather than an etiological (“is cirrhosis a risk factor for avascular necrosis?”).

5. Results

5.1 Study 1 – Risk of complications after total hip or knee arthroplasty

Study 1 included 363 cirrhosis patients (59 with a hospital diagnosis for portal hypertension, as defined on page 18) and 109,159 reference patients without cirrhosis that underwent total hip or knee arthroplasty in 1995–2011. Cirrhosis patients were younger (median age 66 vs. 69 year), were more likely to be male (54% vs. 41%), had more comorbidity (37% vs 18% with Charlson Comorbidity Index>0), were more often hospitalized in the year before the total hip or knee arthroplasty (47% vs 23% with >1 hospitalization), and were more often operated under general anesthesia (34% vs. 23%).

5.1.1 Complications

Cirrhosis patients and reference patients had a similar risk of intraoperative complications, whereas cirrhosis patients had an increased risk of postoperative complications: mortality in-hospital or within 30 days post discharge, transfer to an ICU, transfer to a medical department, and of readmission. The impact of cirrhosis was strongest for mortality and transfer to an intensive care unit (Table 5).

Cirrhosis patients with portal hypertension had a higher mortality than cirrhosis patients without portal hypertension (1.7% vs. 1.3%), and a higher risk of transfer to an intensive care unit (1.7% vs. 0.3%). Even those with the mildest cirrhosis had an increased risk of postoperative complications. The aORs for complications were similar to those in the main analysis, when cirrhosis patients without clinically significant hypertension and reference patients were compared: aOR for mortality: 3.6 (95% CI: 1.3–9.8) and aOR for transfer to ICU: 3.1 (95% CI: 0.4–24). These aORs were also similar in cirrhosis patients and reference patients who underwent total hip or knee arthroplasty under regional anesthesia: aOR for mortality: 3.6 (95% CI: 1.1–12) and aOR for transfer to ICU: 5.9 (95% CI: 0.8–45). Finally, cirrhosis patients' probability of having an uncomplicated hip or knee arthroplasty was 81%

(95% CI: 77–85), the corresponding probability in reference patients was 90% (95% CI: 89–90).

Table 5: Absolute risks and adjusted odds ratios (aOR) for complications after hip or knee replacement for cirrhosis- and reference patients

	Cirrhosis patients	Reference patients	aOR*
Intra-operative complications	2.48% (CI: 1.14–4.65)	1.98% (CI: 1.90–2.06)	1.3 (CI: 0.7–2.5)
Mortality in-hospital or within 30 days after discharge	1.38% (CI: 0.45–3.18)	0.38% (CI: 0.34–0.42)	3.9 (CI: 1.5–10)
Transfer to an intensive care unit	0.55% (CI: 0.07–1.98)	0.055% (CI: 0.042–0.072)	5.8 (CI: 1.3–25)
Transfer to a medical department	4.41% (CI: 2.54–7.06)	2.47% (CI: 2.37–2.56)	1.7 (CI: 1.0–2.9)
Readmission within 30 days after discharge	14.9% (CI: 11.4–17.0)	7.84% (CI: 7.68–8.00)	1.8 (CI: 1.3–2.4)

* Adjusted for age, gender, CCI, operation site (hip/ knee), anesthesia type (general/ regional), and number of inpatient hospitalizations in the year before the hip or knee arthroplasty

5.1.2 Readmissions

The increased risk of readmission was due to liver disease, infection or acute renal failure, while there was no excess risk of readmission for cardiovascular disease or venous thromboembolism (Table 6). The 8% of cirrhosis patients that was readmitted in the category ‘other’ were mostly readmission for specific, but numerically insignificant conditions. However, two large groups stood out: 1/3 of the 8% was readmitted under diagnoses for observation for disease (ICD-10: Zxx), and 1/6 was readmitted for periprosthetic infection which is in line with Figure 1 (page 30).

Table 6: Absolute risks and odds ratios for readmission within 30 days post discharge according to disease categories

Disease category	Risk for cirrhosis patients	Risk for reference patients	Confounder-adjusted odds ratio (aOR)*
Infection	1.65% (CI: 0.61–3.56)	0.77% (CI: 0.72–0.83)	1.8 (CI: 0.8–4.2)
Liver disease	2.48% (CI: 1.14–4.65)	0.001% (CI: 0.0005–0.01)	257 (CI: 99–672)
Acute renal failure	0.55% (CI: 0.07–1.98)	0.010% (CI: 0.008–0.011)	3.4 (CI: 0.8–14)
Venous thromboembolism	0.55% (CI: 0.07–1.98)	0.64% (CI: 0.60–0.69)	0.8 (CI: 0.2–3.2)
Cardio vascular disease	0.55% (CI: 0.07–1.98)	0.61% (CI: 0.56–0.65)	0.7 (CI: 0.2–2.9)
Hip dislocation†	0.82% (CI: 0.17–2.40)	0.48% (CI: 0.43–0.52)	1.5 (CI: 0.5–4.8)
Mechanical complications	1.93% (CI: 0.18–2.55)	1.05% (CI: 0.98–1.11)	1.7 (CI: 0.8–3.6)
Other readmissions	8.26% (CI: 5.41–11.1)	4.99% (CI: 4.86–5.12)	1.5 (CI: 1.0–2.2)

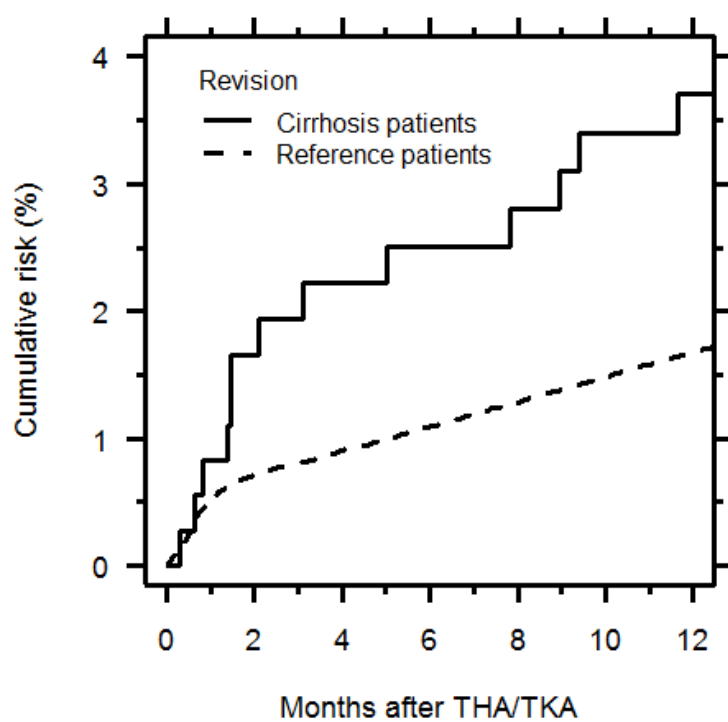
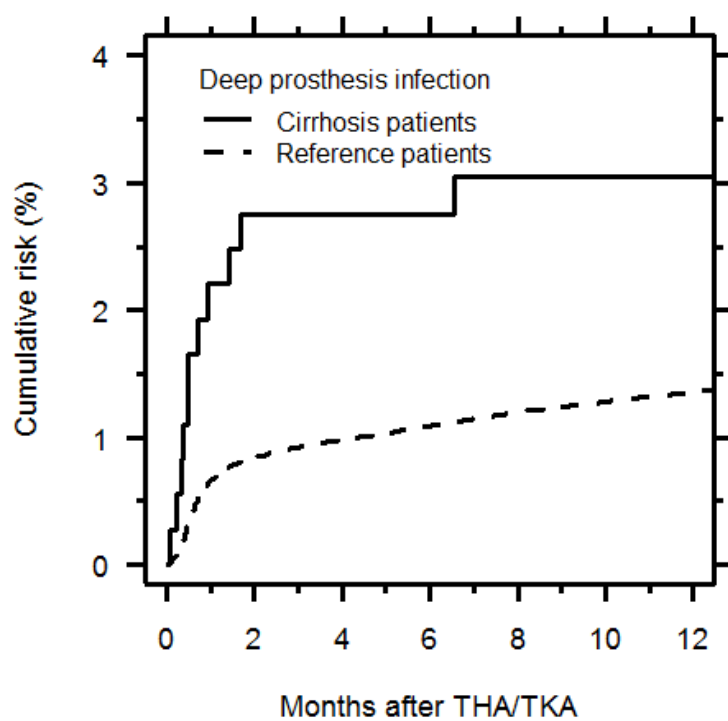
*. aOR are adjusted for age, gender, CCI, operation (hip/ knee), anesthesia (general/ regional) and number of inpatient hospitalizations within the year preceding first hip or knee replacement, †. Including emergency room contacts.

5.1.3 Periprosthetic infection and revision

Cirrhosis patients had a higher 1-year risk of periprosthetic infection than reference patients: 3.1% (95% CI: 1.6–5.2) vs. 1.4% (95% CI: 1.3–1.4). The difference in 1-year risk for cirrhosis patients and reference patients was not explained by differences in age, gender, comorbidity, in-hospital admission, or type of anesthesia: the adjusted subdistribution hazard ratio was 2.1 (95% CI: 1.3–3.7). The majority of periprosthetic infections in both cirrhosis and reference patients occurred during the first two months after the arthroplasty (Figure 1)

Cirrhosis patients were also more likely to undergo a revision arthroplasty than reference patients during the first year after a total hip or knee arthroplasty: 3.7% (95% CI: 2.1–6.1) vs. 1.7% (95% CI: 1.6–1.8). This risk difference was not caused by the listed confounders either: the adjusted subdistribution hazard ratio was 1.9 (95% CI: 1.1–3.3). The revision arthroplasties also clustered in the first two months after the initial arthroplasty, but was otherwise distributed evenly over the remaining first year (Figure 1).

Figure 1 : Cumulative risk of periprosthetic infection or revision



5.2 Study 2 – Risk of primary osteoarthritis

A total of 10,049 cirrhosis patients and 44,370 age-, gender-, and birth date-matched reference persons were included. Their median age was 67 years and 65% were men. The prevalence of COPD on the index date was 10.5% in cirrhosis patients and 4.5% in reference persons.

In total 208 cirrhosis patients and 2,490 reference persons developed primary osteoarthritis of the hip or knee during follow-up. The incidence rate of primary osteoarthritis was 8.40 (95% CI: 7.30–9.63) per 1000 person-year in cirrhosis patients and 8.76 (95% CI: 8.42–9.21) per 1000 person-years in reference persons and the incidence rate was similar for cirrhosis patients and reference persons in all age groups (Table 7). The HR for primary osteoarthritis in the cirrhosis patients vs. the reference persons was 0.99 (95% CI: 0.85–1.16).

There were no signs of effect measure modification: the HR's were similar across all strata. Nor was there any sign that cirrhosis had a distinct effect on the risk of primary osteoarthritis in the hip or the knee. However, when the composite outcome, a diagnosis for primary osteoarthritis *and* a subsequent arthroplasty, was analyzed, the HR for primary osteoarthritis was lower in cirrhosis patients: 0.78 (95% CI: 0.60–1.01).

Table 7: Incidence rates (IR) of primary osteoarthritis of the hip or knee in Danish cirrhosis patients and matched reference persons from the general population

	Age group (years)	Number of patients diagnosed with primary osteoarthritis	Size of population	Follow-up (years)	IR per 1000 person years
Cirrhosis patients	60–69	152	6,634	18,656	8.14 (95% CI: 6.90–9.55)
	70–79	50	2,746	5,592	8.94 (95% CI: 6.63–11.7)
	80+	6	669	783	7.67 (95% CI: 2.81–16.7)
	Total	208	10,049	25,031	8.40 (95% CI: 7.40–9.63)
Reference persons	60–69	1,739	39,658	202,842	9.71 (95% CI: 9.29–10.2)
	70–79	679	11,914	73,789	9.20 (95% CI: 8.52–9.92)
	80+	72	2,798	12,383	5.81 (95% CI: 4.55–7.32)
	Total	2,490	44,370	289,015	8.76 (95% CI: 8.42–9.21)

5.3 Study 3 – Risk of avascular necrosis of the hip

In total, 25,421 cirrhosis patients and 114,052 reference persons were included. Their median age was 57 years and 65% were male. Among them, 45 cirrhosis patients and 44 reference persons underwent total hip arthroplasty for avascular necrosis of the hip during follow-up. The 5-year risk of avascular necrosis was low, but markedly higher in cirrhosis patients than in reference persons: 0.16% (95% CI: 0.12–0.23) vs. 0.02% (95% CI: 0.01–0.03). The prevalence of potential confounders was higher among cirrhosis patients than in reference persons (Table 8).

Table 8: Prevalence of potential confounders to the association between cirrhosis and avascular necrosis (for definitions see Table 3, page 22)

	Cirrhosis patients	Reference persons
Risk factors for avascular necrosis (disease that increase the risk <i>per se</i>)	16%	5%
Indicators for corticosteroid treatment (diseases treated with corticosteroids)	3%	1%
Indicator for smoking (prevalence of COPD diagnoses)	7%	2%

The adjusted hazard ratio for avascular necrosis of the hip in cirrhosis patients vs. reference persons was 10 (95% CI: 5.8–17). The supplementary analysis aimed at minimizing the influence of alcohol intake included 5,040 cirrhosis patients and 22,123 reference patients, but cirrhosis patients' increased HR for avascular necrosis of the hip was essentially unchanged: 12 (95% CI: 3.3–47).

6 Main findings

1. Cirrhosis was a risk factor for postoperative complications after total hip or knee arthroplasty, including mortality, readmission, transfer to medical department or intensive care unit, periprosthetic infection, and revision arthroplasty, but the risk of intraoperative complications was similar for cirrhosis patients and reference patients.
2. Cirrhosis was not a risk factor for primary osteoarthritis, so chronic systemic inflammation does probably not cause primary osteoarthritis.
3. Cirrhosis was a risk factor for avascular necrosis of the hip.

7 Discussion

7.1 Methodological considerations

An important step in all science is to assess the ‘internal validity’. In observational studies, violation of the internal validity is assessed by the extent of selection bias, information bias, confounding and random error (chance). It is important to appreciate that bias and confounding are present in *all* observational studies. The challenge is to minimize their influence on the results by design and/or analysis; and to inform about their presence, size, and direction.

7.1.1. Selection bias

Selection bias arises from the way subjects become eligible to a study (80). The Danish healthcare registries offer an opportunity to study *all* subjects in Denmark diagnosed with a given condition (69, 71). The absence of specific criteria (e.g. having a health insurance) in order to enter work-up and treatment in Danish Hospitals reduces the likelihood of selection bias in studies based on Danish healthcare registers. The possibility to identify an unselected cohort of patients renders studies on Danish nationwide healthcare register data sources (e.g. the NPR) *population-based* (42).

In Study 1, Danish patients that underwent total hip or knee arthroplasty according to the DHR/DKR were studied, but these databases are only 94% and 88% complete, respectively (30, 72). Still, there are no specific eligibility criteria for these databases, and most likely the patients that underwent total hip or knee arthroplasty and are included in the DHR/DKR represent a random sample of all patients that undergo these procedures with no particularly favorable or unfavorable outcome. So, the use of these databases is an unlikely source of selection bias in Study 1.

Study 2 included *all* cirrhosis patients in Denmark that had a hospital diagnosis for cirrhosis when they were aged 60 years or more without risk factors for secondary osteoarthritis.

Study 3 included *all* Danes with a hospital diagnosis for cirrhosis and without risk factors for avascular necrosis of the hip. As reasoned above, the study populations in Study 2 and 3 are a complete sample of *all* Danes with a hospital diagnosis of cirrhosis. The possibility of selection bias in Study 2 or 3 is therefore minimal.

7.1.2 Information bias

Information bias is an error in the measurement of exposure or outcome. It occurs when the exposure or outcome is misclassified. So in this dissertation, misclassification of the exposure is when some of the cirrhosis patients do in fact not have cirrhosis, or some the reference persons do in fact have cirrhosis. Misclassification of the outcome is when some of those who experience an outcome are recorded not to have it, or when persons without the outcome are recorded as having it. Misclassification can be either differential or non-differential. Non-differential misclassification of the outcome occurs when the outcome is misclassified, but the extent of misclassification is independent of the exposure. Non-differential misclassification will bias relative estimates towards the null hypothesis. Differential misclassification occurs when the extent of misclassification is different in exposed and unexposed. Non-differential misclassification can cause bias either towards or away from the null hypothesis.

7.1.2.2 Misclassification of exposure in Study 1, 2, and 3

Cirrhosis was the exposure in all three studies. The positive predictive value of cirrhosis in the NPR is 85% for cirrhosis, and 90% for alcoholic cirrhosis (81). These estimates imply that the 10%–15% of the patients recorded as having cirrhosis do in fact not have cirrhosis. Since the cirrhosis diagnosis was recorded *before* the outcome, it is very unlikely that the extent of misclassification of cirrhosis diagnosis depends on the outcome. Therefore, the misclassification of cirrhosis diagnoses in Study 1–3 is *non-differential* and will bias the relative estimates in these three studies towards the null hypothesis. Therefore, differential misclassification cannot explain Study 1 or Study 3's conclusion. However, the complete

absence of an association in Study 2 could indicate non-differential misclassification. This situation would occur in the unlikely event that the 10–15% with a cirrhosis diagnosis who did not have cirrhosis were at a greatly increased or reduced risk of primary osteoarthritis. Thus, Study 2 conclusion was probably not the result of non-differential misclassification either.

7.1.2.3 Misclassification of the outcome

The outcome in Study 1 was death, transfer between hospital departments, and readmission. The outcome death can be assumed to be 100% valid (70). Also the outcomes transfer between hospital departments, readmission, periprosthetic infection, and revision is unlikely to be misclassified. However, hospital diagnoses are rarely 100% correct. So, there is probably misclassification of readmission diagnosis, but notable differential misclassification in Study 1 is unlikely.

The outcome in Study 2 was a diagnosis for primary osteoarthritis in the NPR. This diagnosis has not been validated, but in the additional analysis which included validated data on the indication from the DHR/DKR, the HR for primary osteoarthritis for cirrhosis patients vs. reference persons was 0.78 (95% CI: 0.60–1.01). There are three possible explanations for this discrepancy: One, compared with reference persons, cirrhosis patients have more false-positive diagnosis codes for primary osteoarthritis in the NPR. Two, cirrhosis patients develop less severe osteoarthritis and do not need arthroplasty. Three, surgeons hesitate to perform arthroplasty in cirrhosis patients. Although the correct explanation(s) remain unknown, the important thing is that the association remains statistically non-significant. Therefore, the possibility of differential misclassification (explanation 1) does not alter Study 2's conclusion: cirrhosis does not cause primary osteoarthritis.

The outcome in Study 3 was a hip arthroplasty with the indication 'avascular necrosis' in the DHR. The outcome was identified in the DHR, because NPR diagnoses for avascular necrosis identifies avascular necrosis at any anatomical site. Moreover, in the DHR the indication avascular necrosis of the hip was confirmed by radiographs or clinical evaluation in 79 out of

80 randomly selected patients (72). Therefore misclassification of the outcome in Study 3 is unlikely.

7.1.3 Confounding

Confounding is an error that occurs when an observed effect of an exposure on the outcome is an effect of another risk factor. Therefore, confounding affects measures of association (relative risk, odds ratios, hazard ratios) and not absolute risks. A confounder must be associated with the exposure and the outcome, and not be a part of the causal pathway. It goes with this description that a confounder must be unevenly distributed among the exposed and the unexposed, and that protective factors can be confounders. Confounding in observational studies is handled in the design phase by *matching* or *restriction*, and/or in the analysis phase by *stratification*, *standardization*, or *adjustment*. Table 9 describes the confounders that was considered for each of Study 1–3, and by which methods (if any) it was attempted to minimize their influence.

Table 9 Possible confounders of cirrhosis' associations with the risk of complications after hip or knee arthroplasty, primary osteoarthritis, and avascular necrosis of the hip; and the methods applied to reduce their influence

	Confounder	Methods
Study 1	Comorbidity	Adjustment for Charlson Comorbidity Index and number of hospitalizations within the previous year
	Age and gender	Adjustment
	Procedure (hip/knee arthroplasty)	Adjustment
	Type of anesthesia (local/general)	Adjustment and restriction
	Year of operation	Adjustment
	Smoking	Indirectly by adjustment for comorbidity, leaving a possibility for residual confounding
Study 2	Alcohol	No method applied
	Age and gender	Matching on age, gender, and birth year
	Smoking (protective factor)	Adjustment for chronic obstructive pulmonary disease.
	Mechanical stress	No method applied
Study 3	Risk factors for secondary osteoarthritis	Restriction to patients without diagnoses for hip fractures or risk factors for secondary osteoarthritis in the NPR, and without a previous hip arthroplasty in the DHR/DKR
	Age and gender	Matching on age, gender, and birth year
	Smoking	Adjustment for chronic obstructive pulmonary disease.
	Corticosteroid treatment	Adjustment for indicators for corticosteroid treatment
	Alcohol intake	Supplementary analysis restricted to cirrhosis patients and reference persons without previous alcohol related diagnoses in the NPR.
	Risk factors for avascular necrosis	Restriction to patients without diagnoses for hip fractures or avascular necrosis in the NPR, and without a previous hip arthroplasty in the DHR

Confounding in Study 1

Both alcohol intake and smoking are associated with an adverse outcome after total hip or knee arthroplasty (82, 83). In Study 1, smoking was indirectly addressed by the adjustment for comorbidity. Alcohol could not be handled by design or analysis, but most likely total hip or knee arthroplasty is offered to cirrhosis patients that abstain from alcohol. Thus, residual confounding from alcohol intake or tobacco smoking, and unknown confounders remains a possibility in Study 1. However, it is unlikely to be the sole explanation to Study 1's results.

Confounding in Study 2

Cirrhosis patients' ascites, energy loss, and general malaise may have resulted in lower physical activity than reference persons, and thus less mechanical stress in weight-bearing joints. If such a 'protective effect' of cirrhosis existed along with a 'risk effect' imposed by chronic inflammation, these two effects had to be exactly similar in *all* gender- and age groups to produce null associations in all strata. That situation is highly unlikely. The use of diagnoses for COPD to identify smokers will underestimate their prevalence, but the absence of an association between cirrhosis and osteoarthritis renders the possibility of confounding from smoking as the main explanation to the study's conclusion unlikely. Still residual confounding from smoking, mechanical stress, and unknown confounders cannot be ruled out.

Confounding in Study 3

Confounding from alcohol was a major concern in Study 3. In the additional analyses aimed at minimizing the influence of alcohol intake, the strong association between cirrhosis and avascular necrosis of the hip ($HR > 10$) was preserved. The evidence of the association between alcohol and avascular necrosis of the hip is derived from two Japanese case-control studies. Interestingly both these studies identified 'liver disease' as risk factor for avascular necrosis of the hip with an adjusted odds ratio of 2.2 and 5.2, respectively (55, 56). Thus, Study 3's conclusion was very unlikely to be the result of residual confounding from alcohol and unknown confounders.

7.1.4 Precision and generalizability

The assessment of bias and confounding in this dissertation three studies has justified their internal validity. However, it is also important to discuss whether the estimates are meaningful in a broader sense. In this context, *precision* and *generalizability* are central concepts.

Precision refers to the influence of chance and random error on the estimates' interpretation. It is measured by the range of the confidence intervals. It is difficult to base clinical decisions on absolute estimates with broad confidence intervals. The large sample size in observational studies based on Danish nationwide healthcare data enables narrow confidence intervals and consequently precise estimates. The possibility to identify a complete sample of Danish patients diagnosed with a given condition implies that these patients are an unselected complete sample of cases from the Danish population (42). Therefore, the absolute estimates from this dissertation are *precise* and can be *generalized* to hospitalized cirrhosis patients in general.

So, in this dissertation the absolute and relative risk estimates are precise and most likely to apply to cirrhosis patients in general because of the population-based design. As argued in the introduction and in the section about methodical considerations, the purpose and the methods in the three studies are sound. These qualities indicate that associations between cirrhosis and the outcome in Study 1 (complications after total hip and knee arthroplasty) and Study 3 (avascular necrosis) imply causality, and the absence of an association between cirrhosis and the outcome in Study 2 (primary osteoarthritis) rejects causality. These conclusions are general statements about the pathophysiology of cirrhosis.

7.2 Comparison to existing literature

7.2.1 Cirrhosis patients' risk of complications after total hip or knee arthroplasty

In Study 1, the association between complications and cirrhosis was difficult to compare with the estimates from previous studies, because only one study provided them. Jiang et al. found a confounder adjusted mortality HR of 3.6 for cirrhosis patients vs. reference patients of 3.6, that underwent knee arthroplasty which is close to the aOR for death in Study 1 (3.9) (39). They also found an HR for readmission after total hip or knee arthroplasty of about 2 which also resembles the findings of Study 1. When I computed the OR for complications in the other Studies, none of these estimates were lower than 4. Thus, there is evidence that

cirrhosis causes an increased risk of complications after total hip or knee arthroplasty even though it is an extra-abdominal procedure performed in an elective setting.

In studies involving intra-abdominal surgery, the odds ratio for 30-day mortality for cirrhosis vs. other patients ranges from 3 to 12 (23, 84-87). The highest odds ratio was for open cholecystectomy and the lowest was for transurethral resection of the prostate (23, 85). So, in the light of Study 1, these results imply that cirrhosis has a similar impact on intra- and extra-abdominal surgery. This is important knowledge, because Study 1 was designed to minimize the influence of assumed causes to cirrhosis patients' intolerance to surgery: dilated and fragile intra-abdominal veins and their inability to excrete and detoxify anesthetic agents. Thus, these disturbances may not be as important as anticipated. Consequently, of the four probably causes to cirrhosis patients increased risk after surgery outlined in the introduction (page 2) only coagulopathy and susceptibility to bacterial infections remain. However, Study 1's results do not indicate that bleeding or thromboembolic events were frequent complications. Therefore, susceptibility to infections appears to be the most important cause of cirrhosis patients increased risk of complications after surgery.

The discrepancy between Study 1's estimates on absolute risks and those from previous studies (Table 1, page 7) probably reflect different patient material and study design, because the previous studies were single-center studies and examined patients treated for various indications including fracture. However, all previous studies agreed that there is an increased risk of renal failure and infection (35-40). Most of the previous studies also indicated that the risk of complications increased with the severity of liver disease (35-38, 40). This was confirmed in Study 1 in which the risk of mortality and transfer to an intensive care unit was higher in patients with portal hypertension (as defined on page 18).

The absolute risk estimates in Study 1 were similar to the corresponding estimates in Jiang et al. This study was based on the experience from total hip or knee arthroplasties in multiple centers, and found an in-hospital mortality of 1% in cirrhosis patients (39). This estimate resembles the mortality in-hospital or within 30 day post discharge of 1.4% in Study 1. They

also found a 180-day risk of periprosthetic infection of approximately 3% in cirrhosis patients. This estimate resembles the corresponding 1-year risk of periprosthetic infections in Study 1 of 3.1%. Hence, it is reasonable to expect that in cirrhosis patients that undergo total hip or knee arthroplasty for other indications than fractures, the postoperative mortality is between 1 and 2%; and that the 1-year risk of periprosthetic infection is 3%.

7.2.2 Cirrhosis as a risk factor for primary osteoarthritis

As argued in the introduction, there are sound reasons to investigate whether chronic systemic inflammation causes primary osteoarthritis. Cirrhosis provided an excellent model for chronic systemic inflammation that could clarify this hypothesis. However, there was no association between cirrhosis and primary osteoarthritis, and the narrow confidence intervals rule out any clinically relevant association. Thus, this finding refutes the hypothesis that chronic systemic inflammation causes primary osteoarthritis of the hip or knee.

7.2.2 Cirrhosis as a risk factor for avascular necrosis of the hip

There was a strong association between cirrhosis and avascular necrosis of the hip. This is in line with Hung et al. that also found a positive —but weaker— association (60). Their study compared cirrhosis patients with other hospitalized patients, and the predominant etiology was hepatitis B. Therefore confounding from alcohol is less likely to influence their result. On the other hand their study had a number of weaknesses that may cause them to underestimate the association: They used hospitalized patients as reference and did not exclude patients with risk factors for avascular necrosis. Despite the weaknesses of Study 3 and Hung et al. (88), the evidence of an association between cirrhosis and avascular necrosis of the hip is reinforced by the presence of a strong association in two different settings.

8 Perspectives

The three studies presented in this dissertation examine the interplay between cirrhosis and diseases of large joints. It contributes with knowledge on several aspects of cirrhosis' pathophysiology.

8.1 Study 1

Study 1 showed that cirrhosis patients have an increased risk of death and complications after total hip or knee arthroplasty. The absolute risk estimates in this study were lower than the estimates from previous studies, but probably more generalizable to the total population of cirrhosis patients owing to the population-based study design.

Study 1 was restricted to patients with primary osteoarthritis. On the one hand, this restriction limits the generalizability of the results to cirrhosis patients' first total hip or knee arthroplasty for this indication. On the other hand, it ensures that all the arthroplasties were performed in an elective setting and that the indication for arthroplasty had minimal impact on the outcome. Consequently, the results in Study 1 imply that the increased risk of death and complications applies to *all* cirrhosis patients, including those with well-compensated cirrhosis. So, even cirrhosis patients in a stable phase of their disease have a profoundly impaired ability to withstand total hip or knee arthroplasty. This finding underlines that the disturbances of cirrhosis extend beyond the abdominal cavity and emphasize that cirrhosis is a *systemic* disease (14).

Study 1 has contributed with two additional findings that improve our understanding of cirrhosis patients' intolerance to surgery:

First, cirrhosis patients' increased risk of death and complications compared with reference patients remained unaltered when the patients operated in general anesthesia were excluded. This finding contradicts previous assumptions about anesthetic agents' detrimental effect in cirrhosis patients (16) and their responsibility for cirrhosis patients' impaired ability to tolerate surgery.

Second, compared with reference patients, cirrhosis patients had an increased risk of infections after total hip or knee arthroplasty. In particular their risk of periprosthetic infections was a matter of concern. More than 3% of cirrhosis patients who undergo total hip or knee arthroplasty develop deep prosthesis infection within one year. In addition, periprosthetic infections in cirrhosis patients are difficult to eradicate, and have a poor outcome (89). Thus, perioperative infection is an important concern in cirrhosis patients that undergo total hip or knee arthroplasty.

Importantly, the study does not directly address the question whether or not to recommend a hip or knee arthroplasty in a cirrhosis patient with primary osteoarthritis. However, it clarifies which aspects to contemplate when a total hip or knee arthroplasty is proposed as treatment for primary osteoarthritis in a cirrhotic patient. The benefits of total hip or knee arthroplasty should be weighed against the risk of immediate complications, and—in the long term—the possibility of a poorly functioning prosthesis. Skou et al. have recently demonstrated that conservative treatment led to clinically relevant improvement in most patients eligible for total knee arthroplasty (34). The clinical improvements were greater in patients randomized to total knee arthroplasty, but they also had more adverse events. Thus, in light of the higher risk of adverse events in cirrhosis patients, conservative treatment may be the most relevant first-line treatment in cirrhosis patients.

Study 1's findings also raise important questions:

1. How does cirrhosis affect surgery in the hip or the knee?

Study 1 indicates that susceptibility to bacterial infections was a cause of complications in cirrhosis patients who underwent total hip or knee arthroplasty, but it is unresolved whether coagulation deficiencies are also involved. An animal model or a prospective study of cirrhosis patients that undergo total hip or knee arthroplasty might clarify the mechanisms.

2. Which cirrhosis patients are at the highest risk of complications?

This question can be answered in a prediction study where all relevant information on cirrhosis patients is included in a regression analysis. The most important requirement for such a model would be to include a measure for the severity of liver disease.

3. Is it possible to prevent complications in cirrhosis patients?

Our findings suggest that infections are an important contributor to the increased risk of complications after total hip or knee arthroplasty in cirrhosis patients. So, it would be informative to do a randomized controlled trial of prevention of infections in cirrhosis patients that underwent this procedure. The intervention could e.g. be pre-operative and/or post-operative rifaximin vs. placebo. Rifaximin may bring down bacterial translocation from the gut and thus prevent immediate complications as well as perioperative infection.

8.2 Study 2

Study 2 indicated that chronic systemic inflammation does not cause primary osteoarthritis. Osteoarthritis is a very prevalent condition, so preventive measures have implications for the public health. Study 2 indicates that such measures should focus on local synovial inflammation rather than systemic inflammation.

Study 2 also raises a question:

1. How can one explain the association between markers for systemic inflammation and symptoms, and symptom progression in primary osteoarthritis, when a causal relation appears to be absent?

In my view the answer may be simple: To establish a causal relation the exposure must occur before the outcome. All these studies of biomarkers for inflammation and primary osteoarthritis have been cross-sectional (48-50). The exposure (elevated serum markers for inflammation), and the outcome (primary osteoarthritis) were recorded at the same instant. So, what these studies showed may be that severe primary osteoarthritis causes systemic inflammation rather than the other way around.

The main objection to Study 2's conclusion may be that it takes decades of chronic systemic inflammation to develop primary osteoarthritis, and cirrhosis patients' high mortality counteracts this development (1, 4). However, this possibility is difficult to settle by studying other inflammatory diseases with a lower mortality, such as inflammatory bowel disease, asthma, or psoriasis. Their systemic inflammation is only present during exacerbations and is modified by their treatment: corticosteroids or monoclonal antibodies that target mediators of inflammation.

8.3 Study 3

Study 3 confirms the findings of Hung et al., a Korean study of cirrhosis patients' risk of avascular necrosis. Such confirmations are important because the evidence of a causal relation is supported by its presence in two independent cohorts. This finding is also supported by the association between 'liver disease' and avascular necrosis of the hip in the two Japanese studies on the association between alcohol intake and avascular necrosis of the hip (55, 56).

As outlined in paragraph 2.3.1 (page 13), cirrhosis' pathophysiology displays a number of features that previously have been linked with avascular necrosis of the hip (10, 26, 65), emphasizing the likelihood of a *causal* relation. In addition fat embolisms have been proposed as the key event in the pathophysiology of avascular necrosis (90), and have been implicated in steroid induced avascular necrosis of the hip (91), as well as liver disease (92). Finally, the common denominator for cirrhosis, HIV, post-transplantation, and corticosteroid treatment is immuno-suppression. So, it is meaningful to theorize that immune-suppression causes avascular necrosis of the hip. This hypothesis could serve as a guideline for future research.

The findings of Study 3 have implications for our understanding of cirrhosis and avascular necrosis of the hip:

- It substantiates the systemic disturbance imposed by cirrhosis, since it by unknown mechanisms alters the homeostasis in the femoral head. The mechanism might be a

combination of endothelial dysfunction, coagulopathy, fat embolism, inflammation, and immunosuppression.

- It also substantiates that avascular necrosis is a multifactorial disease. Although the exact pathophysiology remains unclear, knowledge on risk factors is the first step towards better treatment and prevention.

The findings of Study 3 also have clinical implications.

- Hip pain in cirrhosis patients requires work-up, even in the absence of trauma.
- Both cirrhosis and avascular necrosis increase the risk of complications after total hip or knee arthroplasty.

9 Conclusion

This dissertation has contributed to our understanding of cirrhosis as a systemic disease. In particular cirrhosis patients' impaired immune competence is highlighted as important disturbance. It is likely to be responsible for cirrhosis patients' high risk of complications after total hip or knee arthroplasty. The importance of cirrhosis as a risk factor for avascular necrosis of the hip is also new knowledge, and this association might also be the result of cirrhosis patients' dysfunctional immune system.

The dissertation also questions widespread assumptions: That general anesthesia is an important cause of complication after surgery in cirrhosis patients, and that chronic systemic inflammation is an important risk factor for primary osteoarthritis.

10 Summary

Liver cirrhosis is the end-stage of all chronic liver diseases. It results in a profound disturbance of the homeostasis, and cirrhosis patients have coagulopathy, immune paresis, and chronic inflammation. The consequences of this disturbance on the musculo-skeletal system have not been clarified. Primary osteoarthritis of the hip and knee are prevalent conditions that cause pain and disability. The prevailing treatment for primary osteoarthritis is total hip or knee arthroplasty. It is unclear whether cirrhosis increases the risk of intraoperative and post-operative complications after this procedure. Even though cirrhosis patients have chronic systemic inflammation, and systemic inflammation is assumed to cause primary osteoarthritis, it is unclear whether cirrhosis is a risk factor for primary osteoarthritis. It is also unclear whether cirrhosis causes avascular necrosis, which is an enigmatic condition with an unclear pathogenesis.

The aim of this dissertation was to examine: 1) Cirrhosis patients' risk of complications and mortality after total hip or knee arthroplasty compared to reference patients without cirrhosis 2) Whether cirrhosis is a risk factor for primary osteoarthritis. 3) Whether cirrhosis is a risk factor for avascular necrosis of the hip.

Study 1 included 363 cirrhosis patients and 109,159 reference patients; cirrhosis patients' risk of intra-operative complications was similar to patients without cirrhosis (2.5% vs. 2.0%), adjusted odds ratio: 1.3 (CI: 0.7–2.5); whereas they had a higher mortality in-hospital or within the first 30 days after discharge (1.4% vs. 0.4%), aOR: 3.9 (95% CI: 1.5–10); a higher risk of transfer to an intensive care unit (0.6% vs. 0.06%), aOR 5.8 (95% CI: 1.3–25); transfer to medical department (4.4% vs. 2.5%), aOR: 1.7 (95% CI: 1.0–2.9); and readmission (15% vs. 8%), aOR: 1.8 (95% CI: 1.3–2.4). Within the first year after the arthroplasty, cirrhosis patients had a higher risk of periprosthetic infection (3.1% vs. 1.4%), and higher risk of revision arthroplasty (3.7% vs. 1.7%). These results underline that cirrhosis is a systemic disease with a negative impact on the outcome of surgery, even outside the abdominal cavity.

Study 2 included 10,049 cirrhosis patients older than 60 years at the time of the diagnosis for cirrhosis, and 44,370 age- and gender matched reference persons. The incidence rate of primary osteoarthritis was 8.4 per 1,000 person years among cirrhosis patients and 8.8 per 1,000 person years among reference persons. Accordingly, the incidence rate ratio of primary osteoarthritis for cirrhosis patients compared with reference persons was 0.99 (95% CI: 0.85–1.16). A similar null association was found when this analysis was stratified by age and gender, and when osteoarthritis of the hip or knee were analyzed as separate outcomes. This finding refutes the hypothesis that cirrhosis patients' chronic inflammation causes an increased risk of primary osteoarthritis, and, thus, that systemic inflammation causes primary osteoarthritis in general.

Study 3 included 25,421 cirrhosis patients and 114,052 age- and gender matched reference persons. Among them, 45 cirrhosis patients and 44 reference persons underwent total hip arthroplasty for avascular necrosis. Cirrhosis patients' incidence rate for avascular necrosis was 10-fold increased (95% CI: 5.8–17) compared with reference persons, and their 5-year risk of avascular necrosis was 0.16% vs. 0.02% for reference persons. This finding indicates that cirrhosis is a strong risk factor for avascular necrosis.

In conclusion, cirrhosis is a risk factor for complications after total hip or knee arthroplasty and a risk factor for avascular necrosis, but not for primary osteoarthritis. Thus, cirrhosis imposes a profound disturbance on the entire organism including large joints, but is not a risk factor for the primary osteoarthritis, refuting the hypothesis that systemic inflammation causes primary osteoarthritis.

11 Dansk resume

Levercirrose er slutstadiet af alle kroniske leversygdomme, og forløbet er mærtret af livstruende, indlæggelseskrævende komplikationer.

Cirrose medfører en gennemgribende forstyrrelse af homeostase, og cirrose patienter har kronisk systemisk inflammation. Konsekvenserne for bevægeapparatet er ikke fuldt ud klarlagt. Slidgigt (primær artrose) er en folkesygdom, der medfører smerter og funktionsindskrænkning. Den mest effektive behandlingsform af slidgigt i knæ og hofter er fuld knæ- og hoftealloplastik. Den eksisterende litteratur har ikke klarlagt hvor meget cirrose øger risikoen for intra-operative og postoperative komplikationer efter denne procedure, herunder mortalitet og risikoen for infektion i proteser. Selvom cirrosepatienter har kronisk systemisk inflammation, og systemisk inflammation formodes at kunne forårsage primær artrose er det uafklaret om cirrose kan forårsage slidgigt. Desuden er det uklart om cirrose er en risikofaktor for avaskulær nekrose i hoften, der er en gådefuld lidelse med en uafklaret patogenese.

Formålene med denne afhandling var: 1) At sammenligne cirrose patienters risiko for komplikationer og død efter total hofte og knæalloplastik med risikoen blandt andre patienter uden cirrose, 2) At undersøge om cirrose er en risikofaktor for slidgigt, 3) At undersøge om cirrose er en risikofaktor for avaskulær nekrose.

Disse spørgsmål blev besvaret i tre landsdækkende kohortestudier baseret på data fra Landspatientregistret, kliniske databaser over hofte- og knæalloplastikker og CPR registret.

Studie 1 inkluderede 363 cirrose patienter og 109.159 reference patienter. Cirrosepatienters risiko for intra-operative komplikationer var sammenlignelig med patienter uden cirrose (2,5 % mod 2,0 %), justeret odds ratio: 1,3 (95 % CI: 0,7–2,5); hvorimod de inden for 30 dage efter udskrivelse havde en højere mortalitet (1,4 % mod 0,4 %), OR: 3,9 (95 % CI: 1,5–10) en højere risiko for overførsel til en intensiv afdeling (0,6 % mod 0,06 %), OR: 5,8 (95 % CI: 1,3–25); overførsel til en medicinsk afdeling (4,4 % mod 2,5 %), OR: 1,7 (95 % CI: 1,0–2,9);

genindlæggelse (15 % vs. 8 %), OR: 1,8 (95 % CI: 1,3–2,4) og inden for 1 år havde en højere risiko for proteseinfektion (3,1 % mod 1,4 %) og revision (3,7 % mod 1,7 %). Disse resultater understreger at cirrose er en systemisk sygdom, der har en stor indflydelse på udfaldet af kirurgi.

Studie 2 inkluderede 10.049 cirrose patienter, der var ældre end 60 år på diagnosetidspunktet, og 44.370 alders- og køns-matched reference personer. Incidensrate af primær artrose var 8,4 per 1000 blandt cirrose patienter og 8,8 per 1000 blandt reference personer. Incidensrate ratioen for primær for cirrose patienter sammenlignet med reference personer 0,99 (95 % CI: 0,85–1,16), og det gjaldt uanset om cirrosepatienter og reference personer var opdelt efter alder eller køn, eller hvis vi analyserede hofte- og knæartrose som separate udfald. Studiet afviser altså hypotesen om at cirrose patienters kroniske systemisk inflammation medfører en øget risiko for primær artrose, og altså at systemisk inflammation helt generelt kan forårsage primær artrose.

Studie 3 inkluderede 25.421 cirrose patienter og 114.052 alders- og køns-matched referencepersoner. I alt 45 cirrose patienter og 44 referencepersoner fik lavet hoftealloplastik for avaskulær nekrose. Cirrosepatienters risiko for avaskulær nekrose var 0,16 %, mens referencepersonernes tilsvarende risiko var 0,02 %. Incidensrateratioen for total hoftealloplastik for avaskulær nekrose for cirrose patienter sammenlignet med reference personer var 10 (95 % CI: 5,8–17). Studiet viser at cirrose er en stærk risikofaktor for avaskulær nekrose, men at avaskulær nekrose er en sjælden tilstand, selv hos cirrose patienter.

Samlet set viser studierne at cirrose patienter har en stor risiko for komplikationer når de får lavet knæ- og hofte alloplastik for primær artrose, men at de ikke har en forhøjet risiko for primær artrose på trods af deres kronisk systemiske inflammation. Til gengæld har de en forøget risiko for avaskulær nekrose.

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12 Appendices

Study 1–3

Study 1

Cirrhosis patients have increased risk of complications after hip or knee arthroplasty

A Danish population-based cohort study

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Background and purpose — The risk of complications in cirrhosis patients after orthopedic surgery is unclear. We examined this risk after total hip arthroplasty (THA) or total knee arthroplasty (TKA).

Patients and methods — Using Danish healthcare registries, we identified all Danish residents who underwent a THA or TKA for primary osteoarthritis in the period 1995–2011. We compared the risk of complications in patients with or without cirrhosis.

Results — The surgical technique was similar in the 363 cirrhosis patients and in 109,159 reference patients, but cirrhosis patients were more likely to have been under general anesthesia (34% vs. 23%), were younger (median age 66 vs. 69 years), had a predominance of males (54% vs. 41%), had more comorbidity, and had had more hospitalizations preoperatively. Their risk of intraoperative complications was similar to that for reference patients (2.5% vs. 2.0%), but they had greater risk of dying during hospitalization or within 30 days of discharge (1.4% vs. 0.4%; aOR = 3.9, 95% CI: 1.5–10); greater risk of postoperative transfer to an intensive care unit (0.6% vs. 0.06%; aOR = 5.8, CI: 1.3–25) or a medical department (4.4% vs. 2.5%; aOR = 1.7, CI: 0.99–2.9); greater risk of readmission within 30 days of discharge (15% vs. 8%; aOR = 1.8, CI: 1.3–2.4); and greater risk of deep prosthetic infection (3.1% vs. 1.4%) or revision (3.7% vs. 1.7%) within 1 year. The chance of having an uncomplicated procedure was 81.0% (CI: 76.6–85.0) for cirrhosis patients and 90.0% (CI: 89.6–90.0) for reference patients.

Interpretation — Cirrhosis patients had a higher risk of postoperative complications after THA or TKA for primary osteoarthritis than patients without cirrhosis. This may have implications for orthopedic surgeons' postoperative management of cirrhosis patients, and preoperative assessment by a hepatologist may be indicated.

Liver cirrhosis is the common end stage of all chronic liver diseases, and it affects about 0.2% of the Danish population. Alcohol is by far the most common cause of cirrhosis in Denmark. The number of total hip arthroplasties (THAs) and total knee arthroplasties (TKAs) performed is on the increase. Thus, it is also likely that more cirrhosis patients will undergo THA or TKA, particularly with the growing number of patients with cirrhosis related to obesity and non-alcoholic fatty liver disease. In cirrhosis patients, their portal hypertension, hyperdynamic circulation, and acquired immune deficiency is associated with an increased risk of complications after abdominal surgery (Ziser et al. 1999, Thulstrup et al. 2001, Nielsen et al. 2002, Friedman 2010), but it is unclear whether these patients also have an increased risk of complications after elective THA or TKA. What is known rests on only 4 small studies with selected patients (Hsieh et al. 2003, Shih et al. 2004, Cohen et al. 2005, Moon et al. 2007). They indicated that cirrhosis patients—particularly those with advanced cirrhosis—have an increased risk of developing complications. However, these studies involved patients treated for various conditions, and it is unclear whether the findings also apply to patients treated for osteoarthritis. We therefore examined the risk of complications after THA or TKA for primary osteoarthritis in cirrhosis patients. We expected that the cirrhosis patients would have a higher risk of complications than patients without cirrhosis.

Patients and methods

Sources of data

We performed a historical cohort study that involved linkage of public healthcare registries with clinical databases. All 5.6

million residents of Denmark can be diagnosed and treated free of charge within the tax-funded public healthcare system. The Danish National Patient Registry (NPR) is a nationwide registry of hospital admissions since 1977 and of outpatient and emergency room visits since 1995 (Andersen et al. 1999). The data comprise relevant dates and discharge diagnoses coded in accordance with the International Classification of Diseases, edition 10 (ICD-10) since 1994 and ICD-8 before that. The Danish Hip Arthroplasty Registry (DHAR) and the Danish Knee Arthroplasty Registry (DKAR) hold data on all patients who have undergone a primary or revision THA or TKA in Denmark since January 1, 1995 (DHAR) or January 1, 1997 (DKAR) (Dansk Høftealloplastik Register 2010, Dansk Knæalloplastik Register 2010, Robertsson et al. 2010, Pedersen et al. 2012). Every public and private orthopedics department in Denmark reports to these clinical databases—which are 97% and 92% complete, respectively (Pedersen et al. 2004, 2012). The operating surgeon provides data on the indication for surgery (primary or secondary osteoarthritis, rheumatic arthritis, fracture, congenital hip dysplasia, avascular necrosis of the femoral head, or other indication), type of operation (primary or revision), type of anesthesia (general or regional), antibiotic use, prosthesis components and fixation, intraoperative complications, and revision. Individual-level data from the NPR and the DHAR/DKAR were linked through the unique personal identification number issued by the Danish Central Office of Civil Registration to all Danish citizens at birth or to immigrants. This registry also records the date of death or emigration for all Danish citizens and is continuously updated (Pedersen et al. 2006).

Study population and comorbidity

We included all Danish residents who underwent THA and TKA for primary osteoarthritis between January 1, 1995 and December 31, 2011 according to the DHAR and DKAR, and we only considered their first hip or knee arthroplasty. Those of them who had received 1 or more discharge diagnosis codes for cirrhosis (ICD-10: K70.3, K70.4, K74.6; ICD-8: 571.09, 571.92, 571.99) before the hip or knee arthroplasty were categorized as cirrhosis patients. The remaining patients were categorized as reference patients. Cirrhosis patients were further subcategorized into cirrhosis patients with clinically significant portal hypertension—defined as 1 or more diagnoses with bleeding esophagus varices (ICD-10: I85.0), gastric varices (ICD-10: I86.4), or portal hypertension (ICD-10: K76.6) before the THA or TKA—and cirrhosis patients without portal hypertension. For each cirrhosis patient and each reference patient, we identified all discharge diagnoses in the NPR from in-hospital admissions in the 5 years before the THA or TKA. Using these data, we computed the patient's Charlson comorbidity index (CCI), defined for usage with ICD-10 codes (Quan et al. 2005). Liver disease was not a comorbidity in the present study, and it was therefore excluded from the CCI.

Outcomes and statistical analysis

We computed mortality during hospitalization or within 30 days of discharge, and the risk of complications with corresponding 95% confidence intervals (CIs). Complications included intraoperative complications, transfer to an intensive care unit (ICU), transfer to a medical department, and in-hospital readmission within 30 days of hospital discharge. Using the discharge diagnosis codes shown in Table 3, we further categorized readmissions as being due to infection, liver disease, acute renal failure, venous thromboembolism, cardiovascular disease, hip dislocation, or mechanical complications—or as being due to other diagnoses. In the analysis of readmissions for hip dislocation, we included hospital contacts in outpatient clinics. We used chi-square statistics for categorical variables and Student's t-test for continuous variables to determine whether certain patient characteristics (age, gender, CCI, and number of inpatient hospitalizations in the year preceding arthroplasty) or procedural characteristics (operation site (hip or knee), type of anesthesia (regional or general), and year of operation) differed significantly between cirrhosis patients and reference patients. Logistic regression was used to compute and compare adjusted odds ratios (aORs) of all outcomes for patients with cirrhosis and for reference patients. The odds ratios were adjusted for the patient characteristics and procedural characteristics listed above. We also calculated the probability of an uncomplicated THA or TKA, i.e. the proportion of THAs or TKAs where the patients did not have any of the complications defined above. In addition, we repeated the analyses, restricting them to patients who were operated under regional anesthesia. Furthermore, we compared odds for cirrhosis patients with no clinically significant portal hypertension and for reference patients—regarding mortality during hospitalization or within 30 days of discharge, intraoperative complications, transfer to an ICU, transfer to a medical department, and readmission to hospital within 30 days of hospital discharge. Finally, we computed the cumulative incidence (i.e. risk) of deep prosthetic infection and revision in the first year after THA or TKA using competing-risk methods, with death as the competing risk (Satagopan et al. 2004), and we used competing-risk regression to adjust for the patient and procedural characteristics listed above (Fine et al. 1999). Each patient was followed from the date of THA or TKA for 1 year after this date. Deep prosthetic infection was defined by NPR diagnoses (T84.5, T84.6, and T84.7), and revisions were identified in the DHR or DKR. All statistical analyses were performed using Stata software version 12.1 and R software version 2.14.1 (R Core Team 2013).

Results

We included 363 patients with cirrhosis (59 of them with a history of clinically significant portal hypertension) and 109,159 reference patients who underwent THA or TKA for primary

Table 1. Characteristics of the patient cohort

	Cirrhosis patients	Reference patients	p-value ^a
Number of cases	363	109,159	
Median age, years	66	69	< 0.01
25th and 75th percentiles	59–71	62–76	
M/F, %	54/46	41/59	< 0.01
Hip/Knee, %	58/42	61/39	0.2
Charlson comorbidity index, %			< 0.01
0	63	82	
1	20	11	
2	8	5	
≥ 3	9	2	
Number of inpatient hospitalizations in the year before hip or knee replacement, %			< 0.01
0	53	77	
1	23	15	
2	12	5	
≥ 3	12	3	
Type of anesthesia regional/general, %	34/66	23/77	< 0.01
Year of operation	Data not shown		0.6

^a The p-value represents a comparison between the 2 groups using chi-square test or Student's t-test.

Table 2. Absolute risks (%) and adjusted odds ratios (aORs) for complications after hip or knee replacement in cirrhosis patients and reference patients

	Cirrhosis patients risk (CI)	Reference patients risk (CI)	aOR ^a (CI)
Intraoperative complications	2.48 (1.14–4.65)	1.98 (1.90–2.06)	1.3 (0.7–2.5)
Mortality within 30 days	1.38 (0.45–3.18)	0.38 (0.34–0.42)	3.9 (1.5–10)
Transfer to an intensive care unit	0.55 (0.07–1.98)	0.055 (0.042–0.072)	5.8 (1.3–25)
Transfer to a medical department	4.41 (2.54–7.06)	2.47 (2.37–2.56)	1.7 (1.0–2.9)
Readmission within 30 days	14.9 (11.4–17.0)	7.84 (7.68–8.00)	1.8 (1.3–2.4)

^a Adjusted for age, gender, Charlson comorbidity index, operation site (hip/knee), anesthesia (general/regional), and number of inpatient hospitalizations in the year preceding hip or knee replacement.

osteoarthritis in the period 1995–2011. Cirrhosis patients were generally younger, had male predominance, had more comorbidity, were more frequently hospitalized in the year before THA or TKA, and were more frequently under general anesthesia (Table 1). The median time from diagnosis of cirrhosis to THA or TKA was 6 years and 6 months.

The risk of intraoperative complications was similar for cirrhosis patients and for reference patients (2.48% vs. 1.98%, aOR = 1.3, CI: 0.7–2.5), whereas cirrhosis patients had higher risk of 30-day mortality (1.38% vs. 0.38%, aOR = 3.9, CI: 1.5–9.7), of transfer to an ICU (0.55% vs. 0.055%, aOR = 5.8, CI: 1.3–25), of transfer to a medical department (4.41% vs. 2.47%, aOR = 1.7, CI: 0.99–2.9), and of readmission (14.9% vs. 7.8%, aOR = 1.8, CI: 1.3–2.4) (Table 2). These aORs were essentially unaltered when we restricted our analyses to patients operated under regional anesthesia, or to the 304 cirrhosis patients with no clinically significant portal hypertension. Of the cirrhosis patients, those with clinically significant portal hypertension had higher 30-day mortality (1.7% vs. 1.3%) and risk of transfer to an ICU (1.7% vs. 0.3%) than those without any clinically significant portal hypertension. The excess risk of readmission for cirrhosis patients was due to

infection, liver disease, or acute renal failure, while there was no excess risk of cardiovascular disease or venous thromboembolism (Table 3). Cirrhosis patients had a higher 1-year risk of deep prosthetic infection than reference patients (3.1% (CI: 1.6–5.2) vs. 1.4% (CI: 1.3–1.4)), and the difference remained after adjustment for patient characteristics and procedural characteristics (adjusted subdistribution hazard ratio = 2.1, CI: 1.3–3.7). Moreover, they were more likely to require a revision arthroplasty within a year (3.7% (CI: 2.1–6.1) vs. 1.7%

Table 3. Absolute risks (%) and odds ratios for readmission according to disease categories

Disease category, ICD-10 code	Cirrhosis patients n risk (CI)	Reference patients n risk (CI)	aOR ^b
Infection, DA ^a , DB95 ^a , DB96 ^a , DJ1 ^a , DJ9 ^a , DI0 ^a , DM00 ^a , DN30 ^a , DT814	6 1.65 (0.61–3.56)	843 0.77 (0.72–0.83)	1.8 (0.8–4.2)
Liver disease, DK7 ^a	9 2.48 (1.14–4.65)	11 0.001 (0.0005–0.01)	257 (99–672)
Acute renal failure, DN0 ^a , DN1 ^a	2 0.55 (0.07–1.98)	107 0.010 (0.008–0.011)	3.4 (0.8–14)
Venous thromboembolism, DI80 ^a , DI81 ^a , DI82 ^a , DI83 ^a , DI26 ^a	2 0.55 (0.07–1.98)	702 0.64 (0.60–0.69)	0.8 (0.2–3.2)
Cardio vascular disease, DD65, DI60–DI64, DG45, DI2 ^a	2 0.55 (0.07–1.98)	666 0.61 (0.56–0.68)	0.7 (0.2–2.9)
Hip dislocation ^c , DS73 ^a , DS83 ^a	1 0.82 (0.17–2.40)	279 0.48 (0.43–0.52)	1.5 (0.5–4.8)
Mechanical complications, DT840, DT841, DT842, DT843, DT844	7 1.93 (0.18–2.55)	1,145 1.05 (0.98–1.11)	1.7 (0.8–3.6)
Readmissions with other diagnoses, any other diagnosis	30 8.26 (5.41–11.1)	5,444 4.99 (4.86–5.12)	1.5 (1.0–2.2)

^a Any number.

^b Confounder-adjusted odds ratio (aOR) are adjusted for age, gender, CCI, operation (hip/knee), anesthesia (general/regional), and number of inpatient hospitalizations in the year preceding first hip or knee replacement.

^c Including emergency room contacts.

(CI: 1.6–1.8)). This association remained after adjustment (adjusted subdistribution hazard ratio = 1.9, CI: 1.1–3.3). The probability of having an uncomplicated hip or knee arthroplasty was 81% (CI: 77–85) for cirrhosis patients and 90% (CI: 89.6–90.0) for reference patients.

Discussion

This nationwide registry-based historical cohort study showed that cirrhosis patients who underwent total hip or knee arthroplasty for primary osteoarthritis had a higher risk of dying, of postoperative transfer to an ICU or a medical department, of readmission, of revision, and of deep prosthetic infection than reference patients who underwent the same procedures. However, the majority (81%) of the cirrhosis patients did not have any complications and they did not have an increased risk of intraoperative complications. Cirrhosis patients had a particularly high risk of readmission for infection, liver disease, or acute renal failure.

The strengths of our study were the nationwide population-based design, the large size, and the complete follow-up in a uniform healthcare system. However, one limitation was that we did not assess the validity of our data sources. Between 1996 and 2009, the completeness of the DHR increased from 92% to 97% and the completeness of the DKR increased from 86% to 92% (Dansk Hoftealloplastik Register 2010, Dansk Knæalloplastik Register 2010). We have no reason to believe that the few unregistered procedures involved cirrhosis patients with a particularly favorable or unfavorable outcome. The validity of cirrhosis diagnoses registered in the NPR is 85% (Vestberg et al. 1997), and erroneous diagnoses would have caused us to underestimate the excess risk for cirrhosis patients. The same bias would occur if outcome data were incorrect. It is possible that surgeons are less likely to report intraoperative complications in cirrhosis patients because they accept it as normal to have some difficulty with these patients. If so, this bias might explain the lack of association between cirrhosis and intraoperative complications. All other complications were identified in independent data sources, and we believe that it would be unlikely for them to have been affected by reporting bias, although we have no validation. The validity of the mortality data originating from the Danish Central Office of Civil Registration is essentially 100% (Pedersen et al. 2006).

Another limitation of the present study was the lack of data on alcohol intake and smoking, both of which are associated with a worse outcome after elective surgery (Nath et al. 2010, Singh 2011). There is an obvious association between alcohol intake and cirrhosis, and it is likely that smoking is also more common in cirrhosis patients. Alcohol intake increases the risk of infection in cirrhosis patients (Rosa et al. 2000), but we believe that THA and TKA are mainly offered to cirrhosis patients who do not drink alcohol. Finally, the confounding effect of smoking is indirectly covered by our adjustment

for chronic obstructive pulmonary disease and cardiovascular disease. Thus, alcohol and smoking may have contributed to the association between cirrhosis and postoperative complications, but we do not believe that it fully explains it.

A final limitation of this study was the lack of detailed data on the etiology of cirrhosis and on its severity. We suspect that most of the cirrhosis patients did in fact have alcoholic cirrhosis (Sørensen et al. 2003), so we chose to report outcomes jointly for all cirrhosis patients. The patients were presumably in a compensated stage of their liver disease because the preoperative evaluation for such elective surgery would have identified and excluded patients with gross decompensation. Thus, our results indicate that even cirrhosis patients with a low perceived surgical risk have an increased risk of postoperative complications. This interpretation is supported by our finding that the cirrhosis patients with no clinically significant portal hypertension and those operated under regional anesthesia had an increased risk of postoperative complications. However, it is still meaningful to expect the risk to increase with the severity of the liver disease, in line with the previously reported higher risk according to the severity of portal hypertension (Hsieh et al. 2003, Moon et al. 2007).

Our findings agree with the results of the 4 previously published studies on cirrhosis patients who underwent THA or TKA, and 2 of them even found an increased risk of postoperative infections and acute renal failure (Hsieh et al. 2003, Cohen et al. 2005). Direct comparison is precluded by differences in indications for hip or knee arthroplasty and in patient selection. The latter difference is suggested by the markedly higher 30-day mortality estimates in the other studies (7–10% as opposed to 1.38% in the present study) (Cohen et al. 2005, Moon et al. 2007).

In other types of surgery, odds ratios for 30-day mortality for cirrhosis patients relative to population controls have ranged from 3 to 12 (Poulsen et al. 2000, Nielsen et al. 2001, Thulstrup et al. 2001, Nielsen et al. 2002, Lund et al. 2003, Arif et al. 2012), the lowest odds ratio being for transurethral resection of the prostate (Nielsen et al. 2001) and the highest being for open cholecystectomy (Thulstrup et al. 2001). So, although THA and TKA are extra-abdominal procedures performed in an elective setting, the relative increase in mortality ascribed to cirrhosis is comparable to that seen after other types of surgery. This indicates that the cirrhosis-related excess risk is a systemic problem and is not restricted to intraperitoneal procedures. However, the present study did not address the question of whether cirrhosis patients with primary osteoarthritis should or should not be offered surgery; we merely provide the basis for an informed decision.

The mechanisms behind the increased surgical risk in cirrhosis patients are the subject of debate. Circulatory instability introduced by anesthesia has been proposed (Friedman 2010), but our estimates were unaltered when we excluded patients who were operated under general anesthesia, and this clearly indicates that other mechanisms contribute. Our find-

ings rather implicate susceptibility to bacterial infections in cirrhosis patients as an important cause of their higher risk of having complications after surgery (Christou et al. 2007). In fact, a recent study of patients undergoing THA or TKA identified comorbid liver disease as the strongest predictor of deep prosthetic infection, increasing the odds 2.5-fold (Poultides et al. 2013), and prosthetic hip infections in cirrhosis patients are difficult to eradicate (Hsieh et al. 2010). Suggested mechanisms for this susceptibility include translocation of bacteria from the intestines, dysfunction of polymorphonuclear leukocytes, complement deficiency, and disturbance of the reticuloendothelial system (Møller et al. 2007). 2 studies have shown excessive activation of IL-6 and TNF- α in cirrhosis patients after surgery, and a subsequent acute-phase response (Sato et al. 1996, Lan et al. 2003); this hyperactivity offers a supplementary explanation for the increased surgical risk in cirrhosis patients. Thus, a number of different explanations for the higher surgical risk are possible, and the present study indicates that an increased susceptibility to infection is one of them—while intolerance to anesthesia is of minor importance.

In conclusion, cirrhosis patients undergoing total hip or knee arthroplasty for primary osteoarthritis have an increased risk of dying, of transfer to an ICU or a medical department, of deep prosthetic infection, of revision, and of readmission for infection, liver disease, or acute renal failure. Our results indicate that the risk applies to all cirrhosis patients and not only to severe cases. This may have implications for orthopedic surgeons' degree of preoperative awareness of even discrete signs of cirrhosis, and for the level of attention paid to liver-related problems.

TD, PJ, SO, and HV planned and designed the study. TD and PJ performed the analyses and drafted the manuscript. All the authors reviewed and approved the submitted version of the manuscript.

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Study 2

No increased risk for primary osteoarthritis in liver cirrhosis– a Danish nationwide cohort study

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Abstract

Objective: Chronic synovial inflammation causes primary osteoarthritis, but it is unknown whether chronic systemic inflammation does, too. Patients with cirrhosis have chronic systemic inflammation and therefore we examined the association between cirrhosis and primary osteoarthritis of the hip and knee.

Methods: In Danish healthcare databases we identified all residents over 60 years diagnosed with cirrhosis in 1994–2011, and for each of them we sampled five age- and gender-matched reference persons from the general population. We excluded everyone with risk factors for secondary osteoarthritis and computed incidence rates of a primary osteoarthritis of the hip or knee. We used stratified Cox regression to estimate the hazard ratios (HR) of primary osteoarthritis for cirrhosis patients vs. reference persons in strata defined by gender and age, and we also computed separate HRs for primary osteoarthritis in the hips or knees.

Results: We identified 10,049 cirrhosis patients. Their median age was 67 years, and 65% were men. Among the cirrhosis patients the crude incidence rate of primary osteoarthritis was 8.40 (95% CI: 7.30–9.63) per 1000 person-years. The rate was similar in the reference persons: 8.76 (95% CI: 8.43–9.12) per 1000 person-years. Accordingly, the HR for primary osteoarthritis for cirrhosis patients vs. reference persons was 0.99 (95% CI: 0.85–1.16), and we found the same null association in all patient strata, and in both joints.

Conclusion: Cirrhosis, and thus chronic systemic inflammation, is not a risk factor for primary osteoarthritis.

Key indexing terms: Inflammation; end-stage liver disease; association studies; risk factors

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Running title: Cirrhosis patients' risk of OA

Introduction

Osteoarthritis causes pain, stiffness, and reduced physical activity and quality of life¹. Secondary osteoarthritis has a well-known etiology such as sequelae to trauma, congenital abnormalities, infection, or rheumatoid arthritis, whereas primary osteoarthritis is defined by absence of such previous pathology. Like old age and biomechanical stress, localized joint inflammation is a risk factor for primary osteoarthritis², and we hypothesized that also chronic systemic inflammation increases the risk of primary osteoarthritis³. This possibility is supported by studies linking raised serum markers for inflammation with radiographic changes, symptoms, and symptom progression in primary osteoarthritis^{4,5}. Cirrhosis is the end-stage of all chronic liver diseases and characterized by chronic systemic inflammation⁶. Thus, cirrhosis patients offer an opportunity to study chronic systemic inflammation as a risk factor for primary osteoarthritis, and this has not been examined before. Given this background, our objective was to examine cirrhosis as a risk factor for primary osteoarthritis of the hip or knee.

Patients and methods

Data sources

We performed a nationwide registry-based historical matched cohort study set in the country of Denmark, which has 5.6 million inhabitants. All Danish residents are provided universal, tax-paid access to hospitals. The Danish National Patient Registry (NPR) is a nationwide registry that covers admissions to non-psychiatric hospitals after 1977, and outpatient and emergency room visits after 1995. The data includes relevant dates and discharge diagnoses coded in accordance with the International Classification of Diseases, edition 10 (ICD-10) from 1994 and the ICD-8 before that⁷. The Danish Hip Arthroplasty Registry (DHR) covers all total hip arthroplasties (THA) in

Denmark since 1 January 1995, and the Danish Knee Arthroplasty Registry (DKR) covers all total knee arthroplasties (TKA) in Denmark since 1 January 1997^{8,9}. These clinical databases include the indication for arthroplasty (primary osteoarthritis, or other indication)^{8,9}. The Danish Central Office of Civil Registration continuously monitors Danish residents' vital status including dates of emigration or death and issues a unique personal identifier to all residents in Denmark at birth or immigration. This number enables linkage of individual-level data between the NPR, the DHR/DKR, and the civil registration system¹⁰.

Cirrhosis patients and reference persons

Primary osteoarthritis mainly affects the elderly, so we restricted the study to people aged 60 years or older. First, we identified all Danish citizens with a hospital discharge diagnosis of alcoholic cirrhosis (ICD-10: K70.3, K70.4) or unspecified cirrhosis (ICD-10: K74.6) between 1994 and 2011 in the Danish National Patient Registry (NPR). We defined the 'index date' as the date of their first cirrhosis diagnosis, and identified cirrhosis patients aged 60 years or more on the index date. Among them, we excluded cirrhosis patients who before the index date had a diagnosis for primary osteoarthritis (M16.xx, M17.xx, ICD-8: 713xx) or for a condition predisposing to secondary osteoarthritis (Supplementary Table A), or who had already undergone THA/TKA. All the remaining cirrhosis patients were included. Cirrhosis patients with ascites may have an increased load in weight bearing joints. Therefore, the cirrhosis patients were subdivided into those who on or before the index had a diagnosis for ascites (ICD-8: 785.39, ICD-10: R18) or a procedure code for a paracentesis (ICD-10: KTJA10) and those without. We matched the cirrhosis patients 1:5 on age, gender and birth year to persons without cirrhosis from the general Danish population, using risk

set sampling ¹¹, and these reference persons were given the same index date as their corresponding cirrhosis patient. Subsequently, we applied the same exclusion criteria to the reference persons as to the cirrhosis patients, so not all cirrhosis patients were matched 1:5 in the analysis (60% were matched 1:5, and 92% were matched with 4 or more reference persons).

Primary osteoarthritis

We examined two outcomes: First, time to a first-time hospital diagnosis for primary osteoarthritis of the hip or the knee (ICD-10: M16.0, M16.1 or M17.0, M17.1) according to the NPR. Second, in order to ensure that everyone had equally severe osteoarthritis and that diagnoses were correct, we defined a composite outcome: time to a diagnosis for osteoarthritis of the hip or knee in the National Patient Registry *and* a subsequent THA/TKA for primary osteoarthritis at the same site (hip/knee) according to the DHR/DKR.

Statistical analysis

We followed the cirrhosis patients and the reference persons from the index date to the date of their first diagnosis for primary osteoarthritis, death, or end of follow-up on 31 December 2011. When we analyzed the composite outcome (NPR diagnosis of primary osteoarthritis *and* a subsequent THA/TKA), we followed the cirrhosis patients and their reference population to the date of THA/TKA. We computed crude incidence rates of primary osteoarthritis of the hip or knee for cirrhosis patients and reference persons. Cox regression was used to estimate the hazard ratio (HR) of primary osteoarthritis for cirrhosis patients vs. reference persons. We computed HRs within subgroups defined by gender, age on the index date (60–69, 70–79, >79 years), and for

cirrhosis patients with and without ascites. We also computed separate HRs for primary osteoarthritis in the hip or knee, and for the composite outcome. Smoking may protect against primary osteoarthritis¹², so we adjusted the HRs for previous hospital admissions for chronic obstructive pulmonary disease (ICD-8: 490.xx, 491.xx, 492.xx; ICD-10: J43.x, J44.x). All statistical analyses were performed using Stata version 12.1 (StataCorp, College Station, Texas) and R version 2.14¹³.

Results

We included 10,049 cirrhosis patients and 44,370 matched reference persons. Their median age was 67 years, 65% were male, and 33% had ascites; 10.5% of the cirrhosis patients and 4.5% of the reference persons had chronic obstructive pulmonary disease. A total of 208 cirrhosis patients and 2,490 reference persons were diagnosed with primary osteoarthritis of the hip or knee during the follow-up. Among the cirrhosis patients the crude incidence rate of primary osteoarthritis was 8.40 (95% CI: 7.30–9.63) per 1000 person-years and 8.76 (95% CI: 8.43–9.12) per 1000 person-years among the reference persons; the incidence rates were similar in cirrhosis patients and reference persons in all age groups (Table 1). As we anticipated, chronic obstructive pulmonary disease was associated with a reduced rate of primary osteoarthritis (HR for persons with and without chronic obstructive pulmonary disease = 0.69, 95% CI: 0.53–0.90), but even when we adjusted the osteoarthritis rates for chronic obstructive pulmonary disease's confounding effect, cirrhosis remained unassociated with primary osteoarthritis (HR ratio for cirrhosis vs. reference persons = 0.99, 95% CI: 0.85–1.16). This HR was similar across gender and age groups, for cirrhosis patients with and without ascites, and when we analyzed primary osteoarthritis of the hip or the knee separately (Table 2). However, the HR for the composite outcome for cirrhosis patients vs.

reference persons was 0.78 (95% CI: 0.60–1.01) which may indicate that even though cirrhosis patients and reference persons have a similar rate of osteoarthritis, cirrhosis patients are less likely to undergo THA/TKA for primary osteoarthritis. Probably since orthopedic surgeons hesitate to perform arthroplasty in cirrhosis patients, or since cirrhosis patients have less severe osteoarthritis than reference persons.

Discussion

In this nationwide cohort study we found that cirrhosis was not a risk factor for primary osteoarthritis, and the narrow confidence interval ranging from 0.85 to 1.16 virtually rules out a clinically relevant association.

The strength of our study is its foundation in the Danish health-care data which enables precise estimates, complete follow-up, and a population-based design. The main limitation is the uncertainty regarding the validity of the registry-based exposures and outcomes. We have previously confirmed the cirrhosis diagnosis by biopsy or clinical evaluation in 85% of the cases in the NPR¹⁴, and we find it unlikely that the 15% without cirrhosis in our patient cohort caused us to miss an existing association; that could only happen if all those 15% possessed a factor that confers a greatly reduced (or increased) risk of primary osteoarthritis, and that is highly unlikely. The NPR diagnoses for primary osteoarthritis have never been validated, but we corroborated our results by combining diagnoses for primary osteoarthritis in the NPR with data on the indication for arthroplasty from the DHR/DKR. The validity of the indication 'primary osteoarthritis' in the DHR is 85%⁹, and we assume that the validity of this indication is similar in the DKR. We expect the

validity to be the same for cirrhosis patients and reference persons. So, we do not believe that inadequacies of our data sources impaired the reliability of our results.

The most important risk factor for primary osteoarthritis is old age, and this potential confounder was eliminated by the matching. We also adjusted for a crude indicator for smoking, but the use of hospital diagnosis codes for chronic obstructive pulmonary disease will underestimate the influence of smoking. So if cirrhosis patients' higher prevalence of smoking decreases their risk of primary osteoarthritis, we may underestimate the hazard ratio slightly. Mechanical stress is also a potential confounder. We had no data on body mass index (BMI), and cirrhosis patients' fluctuating volume of ascites fluid makes their BMI a poor marker of mechanical stress. Yet, the HR for primary osteoarthritis was similar for cirrhosis patients with and without ascites. Thus, we find it unlikely that cirrhosis patients experience so much less (or more) mechanical stress that it concealed an association between cirrhosis and primary osteoarthritis. So, although we cannot exclude confounding completely, we do not believe that it explained our results.

There is strong evidence that cirrhosis patients suffer from chronic systemic inflammation⁶, so the absence of an association between cirrhosis and primary osteoarthritis refutes our hypothesis that chronic systemic inflammation causes primary osteoarthritis. Previous studies have found that biomarkers for inflammation (Interleukin-6 and Tumor Necrosis Factor α) are elevated in alcoholic cirrhosis patients and predict increasing knee pain in patients with primary osteoarthritis^{4, 5, 15}.

One way to unite those findings with ours is to posit that it takes decades of systemic inflammation to develop primary osteoarthritis. Cirrhosis patients do not survive long enough to settle that possibility¹⁶, but patients with less life-threatening chronic inflammatory diseases, such as asthma or inflammatory bowel disease, are not good models, either; their systemic inflammation is only active during exacerbations.

From a clinical point of view, the lack of an increased risk for osteoarthritis in cirrhosis is valuable information, because we have shown that hip- and knee arthroplasty in such patients carry an increased risk for postoperative complications¹⁷. The increased risk of complications may imply that surgeons are less willing to do arthroplasties in cirrhosis patients, and it is the best explanation to the slightly lower rate of arthroplasty for osteoarthritis in the cirrhosis patients than in the reference persons.

In conclusion, cirrhosis was not associated with primary osteoarthritis of the hip and knee. This result refutes the hypothesis that chronic systemic inflammation causes primary osteoarthritis.

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Table 1: Incidence rate (IR) of primary osteoarthritis of the hip or knee in Danish cirrhosis patients and age- and gender-matched reference persons from the general population

	Age group (years)	Number of patients diagnosed with primary osteoarthritis	Size of population	Follow- up time (years)	IR per 1000 person years
Cirrhosis patients	60–69	152	6,634	18,461	8.23 (95% CI: 6.97–9.65)
	70–79	50	2,746	5,515	9.06 (95% CI: 6.72–11.9)
	80+	6	669	771	7.78 (95% CI: 2.86–16.9)
	Total	208	10,049	25,031	8.40 (95% CI: 7.30–9.63)
Reference persons	60–69	1,739	29,658	199,273	8.73 (95% CI: 8.32–9.14)
	70–79	679	11,914	72,424	9.37 (95% CI: 8.68–10.1)
	80+	72	2,798	12,259	5.87 (95% CI: 4.59–7.39)
	Total	2,490	44,370	289,015	8.76 (95% CI: 8.43–9.12)

Table 2: Hazard ratio (HR) for primary osteoarthritis for cirrhosis patients vs. reference persons by gender, age on index date, ascites, and site

	HR*
Overall	0.99 (95% CI: 0.85–1.16)
Gender	
Males	0.97 (95% CI: 0.79–1.20)
Females	1.02 (95% CI: 0.82–1.28)
Age group	
60–69	1.02 (95% CI: 0.85–1.22)
70–79	0.94 (95% CI: 0.69–1.29)
80+	0.93 (95% CI: 0.38–2.31)
Ascites	
Yes	0.80 (95% CI: 0.60–1.07)
No	0.97 (95% CI: 0.84–1.14)
Site	
Hip	1.17 (95% CI: 0.95–1.44)
Knee	0.92 (95% CI: 0.74–1.14)
Composite outcome†	0.78 (95% CI: 0.60–1.01)

*Adjusted for chronic obstructive pulmonary disease

†A diagnosis for primary osteoarthritis of the hip or knee *and* a subsequent THA/TKA for primary osteoarthritis.

Supplementary Table A: Causes of secondary osteoarthritis of the hip or knee

Disorder	ICD-8	ICD-10
Avascular necrosis	-	M87.0
Calve-Legg-Perthes	722.11	M91.1
Congenital hip dislocation	755.69	Q65.x
Epifysiylisis	722.10	M93.0
Fracture of distal femur, patella, or proximal tibia	821.xx,822.xx,823.xx	S82.0,S82.1
Hip fracture, acetabulum fracture	820.xx	S32.4,S32.5,S72.x
Hip dislocation, knee dislocation	835.xx,836.xx	S73.x, S83.x
Rheumatoid arthritis, other arthritis	710.xx,711.xx,712.xx,714.xx,715.xx	M0x.x,M10.x,M11.x,M12.x, M13.x,M14.x

Study 3

Cirrhosis is a risk factor for avascular necrosis of the hip – a Danish nationwide cohort study

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Abstract

Background and purpose: There is limited data on risk factors for avascular necrosis of the hip, but cirrhosis has been proposed as a risk factor. We examined the association between cirrhosis and avascular necrosis of the hip.

Methods: We used nationwide health care data to identify all Danish residents diagnosed with cirrhosis in 1994–2011 and matched them 1:5 by age and gender to non-cirrhotic reference persons from the general population. We excluded persons with a previous total hip arthroplasty, hip fracture, or diagnosis for avascular necrosis. The outcome was time to total hip arthroplasty for avascular necrosis. We used stratified Cox regression to estimate the hazard ratio for cirrhosis patients vs. controls adjusted for potential confounders, and we used the cumulative incidence function to compute 5-year risks.

Results: We included 23,505 cirrhosis patients and 99,781 reference persons. Their median age was 57 years, and 65% were men. 41 cirrhosis patients and 41 reference persons underwent total hip arthroplasty for avascular necrosis. Cirrhosis patients' HR for avascular necrosis was 9.4 (95% CI: 5.3–16.6), yet their 5-year risk of avascular necrosis was only 0.15%. For the reference persons, the five-year risk was 0.02%.

Interpretation: Cirrhosis is a strong risk factor for avascular necrosis of the hip, but it remains a rare condition even in cirrhosis patients.

Introduction

Cirrhosis is the end-stage of all chronic liver diseases. It leads to a profound disturbance of the systemic circulation (Vallance and Moncada 1991), the immune response (Lin et al. 2007), and the coagulation system (Northup and Caldwell 2013), but whether cirrhosis is a risk factor for joint disease has not been clarified. Avascular necrosis (AVN) is bone necrosis caused by insufficient circulation, predominantly affecting bone parts with frail circulation: the femoral head and to a lesser extent the femur condyles and the carpal bones (Chang et al. 1993). The pathogenesis of AVN remains poorly understood, but risk factors include tobacco smoking (Hirota et al. 1993, Matsuo et al. 1988), corticosteroid treatment (Guo et al. 2014), alcoholism (Hirota et al. 1993, Matsuo et al. 1988), fractures (Loizou and Parker 2009), and certain other conditions (Mankin 1992). Hung et al. have reported that cirrhosis may also be a risk factor (Hung et al. 2011). Their study compared the risk of AVN for cirrhosis patients vs. an age-matched cohort of hospitalized patients with a high prevalence of conditions that predispose to AVN, and they may therefore have underestimated the strength of the association. AVN is clinically significant because many AVN patients require total hip arthroplasty (THA), and both AVN and cirrhosis increase the risk of complications after THA (Bergh et al. 2014, Deleuran et al. 2014, Hsieh et al. 2010).

The aim of our study was to investigate the association between cirrhosis and AVN of the hip. This may help us understand the pathogenesis of avascular necrosis, and that is the first step towards preventing or treating the condition without surgery.

Methods

Data sources

We performed this registry-based historical cohort study in Denmark which has 5.6 million inhabitants. All Danish residents are provided universal, tax-paid access to hospitals. The Danish National Patient Registry

(NPR) is a nationwide registry that covers admissions to non-psychiatric hospitals since 1977 and outpatient and emergency room visits since 1995. The data include relevant dates and discharge diagnoses coded in accordance with the International Classification of Diseases, edition 10 (ICD-10) from 1994 and the ICD-8 before that (Lyngge et al. 2011). The Danish Hip Arthroplasty Registry (DHR) is a clinical database of all primary or revision total hip arthroplasties (THA) performed in Denmark since 1 January 1995 (DHR). The data is entered by the operating surgeon immediately after the procedure and includes the indication for arthroplasty (primary osteoarthritis, fracture, congenital hip dysplasia, avascular necrosis, or other indication) (Pedersen et al. 2004). The indication for arthroplasty has previously been confirmed by medical chart review and radiographs in 79 of 80 randomly selected AVN patients (Pedersen et al. 2004). The Danish Central Office of Civil Registration continuously monitors Danish residents' vital status including dates of emigration or death and issues a unique personal identifier to everyone at birth or immigration. This number enables linkage of individual-level data between the NPR, the DHR, and the civil registration system (Pedersen et al. 2006).

Cirrhosis patients and reference persons

We identified all Danish residents with a first-time hospital discharge diagnosis of alcoholic cirrhosis (ICD-10: K70.3, K70.4) or unspecified cirrhosis (ICD-10: K74.6) between 1994 and 2011. Biopsy or clinical evaluation confirmed 85% of diagnoses for cirrhosis in the NPR in a previous validation study (Vestberg et al. 1997). We defined the 'index date' as the date of the first cirrhosis diagnosis. To study the association between cirrhosis and AVN, we excluded cirrhosis patients if they had a previous diagnosis for avascular necrosis (ICD-10: M87.0), if they previously underwent THA, or if they were diagnosed with hip fracture (ICD-8: 820, 821, 822, 823; ICD-10: S72.0, S82.0, S82.1, S83) before the index date. We matched these cirrhosis patients 1:5 by age, gender, and birth day to reference persons without cirrhosis from the general Danish population, using risk set sampling (Langholz and Goldstein 1996), and the reference persons were

given the same index date as their corresponding cirrhosis patient. We excluded reference persons according to the same criteria as cirrhosis patients; this exclusion had the result that not all cirrhosis patients were matched 1:5.

Confounders

The NPR holds data on potential confounders of an association between cirrhosis and AVN. We identified previous emergency room visits, in- and outpatient hospitalizations for conditions predisposing to AVN (diabetes, HIV infection, myeloproliferative disease, hemoglobinopathy, chronic renal failure, gout, solid organ transplantation); an indicator for smoking (chronic obstructive pulmonary disease); and indicators for corticosteroid treatment (autoimmune hepatitis, rheumatoid arthritis, connective tissue disease) (Diagnosis codes shown in Supplementary Table A). As an indicator for alcohol intake we identified previous emergency room visits, in- and outpatient hospitalizations for alcoholism or alcohol-related disorders (Supplementary Table B).

Outcomes and statistical analysis

We examined one outcome: time to first total hip arthroplasty for AVN. We followed cirrhosis patients and the reference persons from the index date to the date of a THA for AVN, death, or end of follow-up on 31 December 2011. We used stratified Cox regression to estimate the hazard ratio (HR) of AVN for cirrhosis patients compared with the reference persons and adjusted these HRs for potential confounders. We used the cumulative incidence function with death as a competing risk to compute the 5-year risk of AVN.

Alcohol intake is a well-known risk factor for AVN, and cirrhosis patients have a high prevalence of alcohol intake. We were concerned that the regression analysis would leave residual confounding, so we performed a supplementary analysis in which we used restriction to minimize confounding by alcohol intake: We repeated the regression analysis and restricted it to cirrhosis patients with unspecified cirrhosis (K74.6) who had not been hospitalized for an alcohol-related disorder (supplementary Table A), and their

corresponding reference persons. Reference persons previously hospitalized for an alcohol related disorder (Supplementary Table A) were also left out of this analysis. All statistical analyses were performed using Stata version 12.1 (StataCorp, College Station, Texas) and R version 2.14 (R 2013).

Results

We included 23,505 cirrhosis patients and 99,781 reference persons. Their median age was 57 years and 65% were male. A total of 41 cirrhosis patients and 41 reference persons underwent total hip arthroplasty for AVN. The prevalence of potential confounding factors for AVN was higher among cirrhosis patients than among reference persons (24% vs. 8%). Cirrhosis patients' adjusted hazard ratio for AVN was 9.4 (95% CI: 5.3–16.6). Both cirrhosis patients' and reference persons' 5-year risk of avascular necrosis was very low, but markedly higher in cirrhosis patients: 0.15% (95% CI: 0.11–0.22) vs. 0.02% (95% CI: 0.01–0.05). Cirrhosis patients' HR for AVN was essentially unaltered in our supplementary analysis restricted to patients without alcoholic cirrhosis (Table 1).

Discussion

We performed a nationwide cohort study and found a strong association between cirrhosis and THA-requiring avascular necrosis. This association was unaltered when we performed a supplementary analysis to minimize the influence of alcohol intake on our results. The absolute risks of AVN were low, but markedly higher in cirrhosis patients than in reference persons.

The primary strength of this study is its population-based design and complete follow-up. A possible limitation is the validity of our data sources. NPR diagnoses for cirrhosis have previously been validated with biopsy or clinical evaluation as gold standard. Cirrhosis was confirmed in 85% of patients with this diagnosis in the NPR (Vestberget al. 1997), and the bias introduced by misclassifying persons without cirrhosis as cirrhosis patients, or vice versa, will cause us to underestimate the true strength of the

association between cirrhosis and AVN. The indication for hip arthroplasty in the DHR has been validated, showing that the positive predictive value for AVN was 99% (Pedersen et al. 2004). Thus, we have no reason to believe that the strong association between cirrhosis and AVN was the result of imperfect data sources.

Incomplete confounder control could potentially have biased our estimates upwards. We were able to adjust for conditions that predispose to AVN and for indicators for smoking and treatment with corticosteroids, but our use of hospital diagnoses to identify confounders will probably underestimate their prevalence. Our results were unaltered when we performed a supplementary analysis aimed at minimizing the effect of alcohol intake. Still, we cannot rule out that some of the association was caused by alcohol intake and other confounders, but we find it unlikely that the strong association was entirely the result of confounding.

Hung et al. found a HR for AVN of 2.53 in a cohort of patients with cirrhosis primarily due to viral hepatitis compared with an age-matched cohort of hospitalized patients without cirrhosis (Hung et al. 2011). These hospitalized patients without cirrhosis had a high prevalence of conditions that predispose to AVN, but the reported associations were only adjusted for conditions recorded at the index hospitalization. Such incomplete recording of confounders may have resulted in residual confounding which would have caused Hung et al. to underestimate the true strength of the association.

The mechanisms behind the association between cirrhosis and AVN are unclear. Cirrhosis patients suffer from coagulopathy, endothelial dysfunction, and chronic inflammation (Albillos et al. 2014, Iwakiri and Groszmann 2007, Sogaard et al. 2009). Endothelial dysfunction has been linked to glucocorticoid-induced AVN (Chen et al. 2013), but chronic inflammation may be more important for AVN development (Morse et al. 2013). Interleukin-33, a T-lymphocyte activator, has been linked to both cirrhosis and AVN (Marvie et al. 2010, Zheng et al. 2014), and cirrhosis patients' hyperdynamic circulation facilitates diffusion of pro-inflammatory cytokines and endotoxins throughout the body (Lee et al. 1996). Hence, even though the

exact mechanisms remain unclear, the pathophysiology of cirrhosis exhibits a number of characteristics that have been linked with AVN, so a causal link from cirrhosis to AVN is plausible.

In conclusion, cirrhosis is a strong risk factor for avascular necrosis requiring total hip arthroplasty.

Fortunately, avascular necrosis is a rare condition, even in cirrhosis patients.

Table 1: Result of the main and the supplementary regression analysis.

	Cirrhosis patients (N)	Reference persons (N)	Number of cirrhosis patients who developed AVN	Number of reference persons who developed AVN	Adjusted hazard ratio of AVN for cirrhosis patients vs. reference persons*
Main analysis	23,505	99,781	41	41	9.4 (95% CI: 5.3–16.6)
Supplementary analysis	4,784	20,136	8	12	8.1 (95% CI: 2.4–27.1)

*Adjusted for potential confounders

Supplementary Table A: Conditions predisposing to AVN, the indicator for smoking, and indicators for corticosteroid treatment with ICD 8 and ICD-10 codes.

	ICD-8	ICD-10
Conditions predisposing to AVN		
Diabetes mellitus	24.9x, 25.0x	E10.x-E14.x
Human Immune Deficiency virus	079.83	B20.x–B24.x
Myeloproliferative disease	20.xx	C88.x, C90–96.x
Hemoglobinopathy	28.2x	D55.x– D59.x
Chronic renal failure	58.xx	N18.x
Gout	27.40	M10.x
Solid organ transplantation	Y95.x	Z94.x
Indicator for smoking		
Chronic obstructive lung disease	490.x–492.x	J43.x–J44.x
Indicator for corticosteroid treatment		
Autoimmune hepatitis	57302	K73.2, K75.4
Rheumatoid arthritis	712.0x–712.2x	M05.x
Connective tissue disease	73.4x	M3x.x

Supplementary Table B: Alcohol-related disorders

Alcohol related disorders	ICD-8	ICD-10
Alcohol induced pseudo-Cushing's syndrome		D24.4
Alcoholic cardiomyopathy		I42.6
Alcoholic gastritis		K29.2
Alcoholic myopathy		G72.1
Alcoholic polyneuropathy		G62.1
Acute alcoholic pancreatitis		K85.2
Chronic alcoholic pancreatitis		K86.0
Degeneration of nervous system due to alcohol		G31.2
Ethanol poisoning		T51.0
Mental and behavioural disorders due to use of alcohol	291.xx,303.xx	F10.0

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