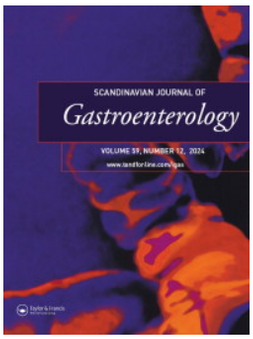

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REVIEW ARTICLE

Forty years of successful national research collaboration in liver disease – the Swedish experience

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ABSTRACT

Aim: Sweden has historically provided a fruitful arena for research in clinical medicine. We here share 40 years of experience of collaboration in the Swedish hepatology research group (SWEHEP) (https://www.swehep.se).

Methods: We describe the way the Swedish hepatology pioneers started the group and how the network continuously developed over the years. Successful projects such as thorough studies of natural history and various clinical aspects of autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, and steatosis are described.

Results: Over the years, more than 80 publications have been published by the group. A summary of new and ongoing research programs includes the randomized placebo-controlled trial of simvastatin in PSC (PiSCATIN), the prospective BIGMAP (Biochemical and genetic markers for the assessment and prognostication of liver cirrhosis) initiative in patients with liver cirrhosis, and the DETECT-HCC, a prospective multicenter cohort study comparing abbreviated MRI and ultrasound for surveillance of hepatocellular carcinoma every six months over two years. The group philosophy, success factors for the longstanding collaboration as well as experience of failures are shared.

Conclusion: The success of hepatology research in Sweden is based on longstanding collaboration over generations of hepatologists, where everyone contributes, regular research meetings, mutual trust, and perseverance.

Abbreviations: AASLD: American Association for the Study of Liver Diseases; AIH: autoimmune hepatitis; EASL: European Association for the Study of the Liver; HFE: homeostatic iron regulator; HR: hazard ratio; MRI: magnetic resonance imaging; PBC: primary biliary cholangitis; PSC: primary sclerosing cholangitis; SILK: Swedish internal medicine liver club; SLK: Swedish liver club (SLK),; SRL: Swedish Registry for Liver Cirrhosis; SWEHEP: Swedish hepatology research group; UCR: Uppsala Clinical Research center; UEG: United European Gastroenterology; UDCA: ursodeoxycholic acid

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Introduction

Being a small country, research collaboration is central in order to compete with international larger and stronger research environments. This has encouraged Swedish researchers in clinical medicine to come together and with joint forces perform medical and clinical studies, also in the field of gastroenterology and hepatology. Hepatology is not a separate specialist education in Sweden, which emphasize the need of collaboration in this field. Research collaborations for clinical trials is currently supported on a national level and the last ten years clinical studies are funded by the Swedish Research council. This is the largest governmental research funding through yearly calls for 'Research environment grant within clinical therapy research'.

All Swedish residents have since 1947 been assigned a unique personal identity number which provides great possibilities to follow people and their diseases over time. This is used in different registries for example the Swedish Population Register, the National Patient Register, the National Cancer Register, the Swedish Multigeneration Register, the Swedish National Causes of Death Register, and the National Prescription Drug Register. This puts Sweden in a unique

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position for epidemiological research but also ensures a minimal loss in the follow-up of patients.

The autoimmune liver diseases, autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC), have for a long time been a major interest and an important focus area for our national research group, Swedish Hepatology Research Group (SWEHEP). We here share forty years of experience of our collaboration leading to important results in this field (www.swehep.se).

How it all began

In the 1960–70ties Swedish gastroenterology lacked behind. Hepatology hardly existed. In Denmark, hepatology was a specialty of its own. A survey among Swedish doctors in 1977 showed that there were only 17 gastroenterologists in Sweden with a modern training. More than half of them worked in the largest cities; Stockholm or Gothenburg. During his service at the Dept. of Infectious Diseases in Linköping 1964 Dr Gunnar Järnerot became interested in hepatology. By time new advances made differential diagnosis more accurate, but Swedish hospitals were not big enough for meaningful hepatology studies. In 1984, the idea to create a national club for hepatologic research emerged, and together with Rolf Olsson in Gothenburg and through economic support from Erik Envall, from the medical company Searle the first meeting took place in Örebro December 5, 1984. The meeting was attended by several leading Swedish gastroenterologists and internists at the time; Rolf Olsson, Gothenburg. Åke Danielsson, Umeå, Sten Eriksson, Malmö, Lars Lööf, Uppsala, Lars Nilsson, Huddinge, Gunnar Järnerot, Örebro, and Peter Rolny, Örebro. At this meeting the Swedish liver club (SLK), later changed to Swedish internal medicine liver club (SILK) was established. Rolf Olsson was elected chairman, which he was until his death in 2008 and Åke Danielsson was the permanent secretary. Various research projects were discussed, such as chronic active hepatitis in Sweden, the epidemiology of primary sclerosing cholangitis in patients with ulcerative colitis and primary biliary cirrhosis. Another aim for SILK was to enhance training and research in hepatology in Sweden.

The number of permanent members never exceeded 10-15, although some of the original members were replaced by others; Ljusk Siw Eriksson, Huddinge, Ola Weiland, Stockholm, Rolf Hultcrantz, Stockholm, Stefan Lindgren, Malmö, Ulrika Broomé, Huddinge, Sven Almer, Linköping, Hanne Prytz, Lund and Hanna Sandberg-Gertzén, Örebro. SILK managed to be efficient and cooperative during the years, which is mainly attributable to the leadership of Rolf Olsson. His lack of prestige, diplomatic ability and enormous knowledge of the current hepatologic literature made him unique. The support from Ulla Thilén from MEDA AB was also for many years of great importance enabling regular meetings.

Further development of the group

Rolf Olsson's death led to a natural generational shift and the group had to reorient itself. Stefan Lindgren was appointed as the new lead and Mårten Werner became the new secretary, and younger investigators were invited to participate. There was pressure from the Swedish Society of Gastroenterology wishing SILK to become more open and gradually the initial liver club SILK transformed into today's research network: the Swedish Hepatology Research Group (SWEHEP). Annika Bergquist replaced Stefan Lindgren as the lead and some formal rules were established (Table 1). At this time, the group also decided to focus on larger prospective high-quality projects.

Table 1. Common rules for SWEHEP.

The group is open for all interested members that want to contribute to science in hepatology and have fun
All ordinary members have a PhD, PhD students are welcome as affiliated members
Every member shall participate or contribute to at least one of the ongoing projects
The ordinary member should be present at all meetings and absence from two consecutive meetings raises the question if the person wants to continue
The meetings are taking place twice a year from a Thursday lunch to Friday lunch
All members should be well prepared before the meetings
The collaborative environment should be characterized by generosity
The group is independent from the Pharma Industry and travels and accommodation is paid by the member

Accomplishments for 40 years

Primary sclerosing cholangitis

Primary sclerosing cholangitis was early identified by Rolf Olsson as an area of interest. The study on colchicine treatment of PSC published in Gastroenterology in 1995, which showed no effect of the drug on survival, symptoms, serum biochemistry, or liver histology, was one of the first large accomplishments of SILK [1]. That was followed by a study using the results from the liver biopsies of the colchicine study, showing that sampling variability using percutaneous biopsies is huge, leading to advanced disease being missed in up to 40% [2]. This study is still frequently cited. Ten years later the next clinical trial 'High-dose ursodeoxycholic acid in primary sclerosing cholangitis: a 5-year multicenter, randomized, controlled study' was published in Gastroenterology which has become one of the landmark studies of ursodeoxycholic acid (UDCA) in PSC [3]. A large cohort of 305 patients with PSC was collected by Ulrika Broome and the natural history was described in a paper in 1995 [4] and later also the natural history of small duct PSC was published [5]. The PSC cohort increased steadily and in 2002 Bergquist published a paper on the increased risk of hepatic and extrahepatic malignancies in primary sclerosing cholangitis showing a 160 times increased risk for bile duct cancer compared to the general population [6]. This was followed by a paper on the risk of PSC and IBD in first-degree relatives with PSC in 2008 indicating a complex inheritance of PSC [7]. In 2012, the prospective study on magnetic resonance imaging (MRI) surveillance for early detection of cholangiocarcinoma was launched and disappointing results were published recently, showing that this strategy does not seem to provide long-term survival in those that develop cholangiocarcinoma. However, only 2% of PSC patients developed cholangiocarcinoma during the 5-year study period [8]. The secondary aim of the surveillance study was to create a large biobank of yearly PSC samples together with clinical data

and yearly MRIs. This opens for studies on new biomarkers in PSC in this cohort, named The Swedish initiative for the study of Primary sclerosing cholangitis (SUPRIM) [9]. Development of a new MRCP based score assessing the severity of PSC, The District Score, is one example of how the SUPRIM cohort have been used [10]. *The SUPRIM cohort is available for collaboration.*

Autoimmune hepatitis

A broad project on AIH was initiated in 1999 by professors Rolf Olsson and Åke Danielsson. The initial aim was to collect data to describe AIH in Sweden and provide epidemiological data on cancer risk, prognostic factors, treatment, and outcome. Among other findings, an overall risk of HCC increased 23 times compared to the general population (SIR 23.28 (95% CI 7.5–54.34) was shown [10]. Worse outcomes with a need for subsequent liver transplantation were associated with cirrhosis at diagnosis, a non-response to initial immune-suppressive treatment or elevated INR values [11]. Furthermore, possibilities and risks in pregnancies for mothers with AIH and their fetus were consequently studied confirming a generally good outcome for the fetus and mothers even in compensated cirrhosis [12, 13]. The cohort today includes more than 1000 individuals with AIH. Nine publications and two doctoral theses have derived [10–18]. *This cohort is open for new research questions.*

Primary biliary cholangitis

Current understanding of PBC pathophysiology, clinical characterization, treatment and prognosis is based on a lot of studies through the years and SILK/SWEHEP have been one among several research groups who contributed to this. Professors Lindgren, Järnerot and Danielsson all published data on prevalence, clinical features and prognosis in local cohorts of PBC during the 1980s [19–21]. Together, within the SILK collaboration a large national cohort of 559 Swedish PBC patients was gathered. Based on this cohort, the presumption that there is an excess risk of breast cancer in PBC was dismissed and risk of liver malignancy was shown to be modest [22]. The risk of ostemalacia and osteoporosis in PBC was another field of study where the authors showed no increased risk in early stages of the disease compared to matched controls [23]. Among other data outcome of pregnancy in PBC and the prevalence of variant forms of PBC has also been reported from this collaboration [24]. In addition, SILK performed one of the original placebo-controlled clinical trials on UDCA treatment for PBC. 116 patients with PBC were randomized to receive either 0.5 g UDCA or placebo daily for 2 years. UDCA improved serum enzyme values but not survival, symptoms, serum bilirubin levels, or liver histology [25].

In more recent years, SWEHEP has gathered a new PBC cohort and Henriksson has shown that both untreated patients and UDCA non-responders have lower liver transplantation-free survival rates than UDCA responders. This study is also the first to show that patients with PBC were more likely to be on sick leave compared to matched controls from the general population [26].

Haemochromatosis

Studies on haemochromatosis were initiated by Rolf Hultcrantz, investigating 3800 cases from national registries and a clinical cohort of 373 cases which were followed in the SILK network. It was found that haemochromatosis patients detected by health check-ups and family screening are younger and with less advanced liver fibrosis [27]. A slightly increased mortality rate [28] and higher risk of hepatocellular carcinoma [29] were demonstrated in the haemochromatosis cases compared to controls or first-degree relatives, but no increased risk för colorectal or breast cancer. This was later verified in a cohort of 3800 patients with the typical homeostatic iron regulator (HFE) gene mutations [30].

Steatotic liver disease

While SWEHEP has traditionally focused on autoimmune liver diseases, interest for studies on steatotic liver disease have recently emerged. In 2012–2015, the first study was conducted, named 'fatty liver in Sweden' (FLIS), examining the impact of alcohol on presumed metabolic dysfunction-associated steatotic liver disease (MASLD). From 120 subjects with biopsy-confirmed steatotic liver disease, 13 (11%) had high levels of phosphatidyl ethanol, a highly specific marker for alcohol consumption [31]. Hence, this was one of the first studies to report that alcohol biomarkers are important to include in the workup of patients with suspected MASLD, and that consumption of alcohol is difficult to ascertain otherwise. This has later been replicated using other biomarkers in larger studies [32].

Supplementary 1 shows a complete publication list from the group.

Failures

AIH bud pred – trial

AIH BUD PRED (EudraCT 2018-003381-14) included its first patient in December 2020, the study was an open-label, prospective randomized multicenter 12-month clinical trial comparing the effect and side-effects of budesonide versus prednisolone as first-line treatment of newly diagnosed non-cirrhotic autoimmune hepatitis. The study was inspired by Manns et al. study which was criticized for its study design [33]. We hoped to clarify the efficacy of budesonide with standardized treatment doses of Budesonide/prednisolone using protocol biopsies at start and at 12 months in treatment naïve patients. Unfortunately, inclusion rate was very slow, which in the beginning we blamed the COVID-19 pandemic. Later, it became clear that with an incidence of 1/100,000 per year combined with the reality of clinical work that the planned recruitment was difficult to achieve. After including 27 individuals with newly diagnosed AIH of whom 20 patients completed the study, we realized that it would be impossible to include the planned 100 patients in reasonable time. Therefore, we decided to stop the recruitment after three and a half years.

Eplerenon trial

In 2011, the aldosterone antagonist eplerenone had become more common in treatment of congestive heart failure and was proposed to reverse the problem with spironolactone induced side effects such as gynecomastia. A Swedish prospective randomized multicenter study of efficacy and endocrinologic side effects comparing eplerenone and spironolactone in male patients with ascites due to liver cirrhosis (EudraCT 2011-001264-22) was initiated. Recruitment of patients started in March 2013 with a goal to include 150 patients. However, after two years only 20 patients had been recruited, mainly at two sites. To be able to evaluate side effects and efficacy, only patients without prior treatment with diuretics during the last three months were eligible. This showed to be the main obstacle for inclusion since patients almost always were given diuretics before contact with a hepatologist. Therefore, the study was decided to be terminated.

Ongoing projects

PiSCATIN. Following the UDCA trial [3] and the prospective MRI surveillance study [8] both the group of researchers and the patients wanted to drive the field forward. UDCA is at this time widely used despite the scarce evidence. Other drugs including immunosuppressants, anti-inflammatory drugs and antibiotics had not shown favorable effects [34–36]. A hypothesis-generating cohort study of Swedish patients with PSC between 2005 and 2014 ($n=2,914$) that were followed-up until 2016 was performed. The risk for death, liver transplantation, variceal bleeding and cancer in relation to different drug exposures of interest including UDCA, immunosuppressants, anti-inflammatory drugs, antibiotics, and statins was tested using data from the Patient Register, the Prescribed Drug Register, the Death Certificate Register and the Cancer Register. Among all the studied drugs, statins were shown to be associated with the lowest risk of death or liver transplantation. In statin users the hazard ratio (HR) for death or liver transplantation was markedly reduced; HR 0.50, 95%CI 0.28–0.66. Based on this data together with the emerging evidence that the use of statins is beneficial in chronic liver disease by lowering the risk for liver failure and reducing mortality [37] we decided to perform a large randomized trial on simvastatin vs. placebo [38]. The study is ongoing and by August 2024, 490 patients have been included (Figure 1).

FLIS-2. A second initiative, the 'FLIS-2' cohort, was initiated in 2017. The cohort includes around 300 patients diagnosed with MASLD that are followed with repeated visits during five years. Fibrosis progression is measured using vibration-controlled transient elastography, and liver biopsies in a subset of patients. Extensive biobanking is performed at the repeat visits, with an overarching goal to develop new and validate existing biomarkers for MASLD severity and progression. A first paper was published in 2024, examining the role of cleavage products from collagen formation and degradation [39]. The study found that such markers only had a slight advantage over existing means to detect liver fibrosis. *Additional studies are ongoing, and the cohort is available for collaborations.*

Bigmap. Liver cirrhosis carries a risk of developing complications such as HCC, acute liver decompensation or portal venous thrombosis. Risk assessments have been mainly carried out in cross-sectional studies, comparing cases with controls, whereas longitudinal follow-up studies are lacking. Therefore, the BIGMAP initiative was started in 2020. BIGMAP (Biochemical and genetic markers for the assessment and prognostication of liver cirrhosis) is a prospective repeated biobanking of plasma, serum and DNA from patients with liver cirrhosis which are monitored within the SWEHEP network. Patients are followed with semiannual ultrasound, yearly blood sampling and clinical evaluation, until transplantation, death, development of HCC or up to 10 years. Apart from the longitudinal sampling, blood is collected at the time of a clinical event (i.e. HCC, PVT or decompensation). Until now, 450 patients have been included, of which 70 cases have an early-stage HCC. We aim to include 1000 patients with cirrhosis and 300 patients with early-stage HCC within the SWEHEP network. The first study will focus on bloodborne biomarkers of HCC, which is planned in 2025–2026. The cohort is available for collaborations.

Detect-hcc. The landscape of liver cirrhosis is changing. Over the last decade, we have observed a steady increase in MASLD cirrhosis, which is now the most common cause of HCC in Sweden [40–42]. Given the strong association between obesity and MASLD, this has significant implications for HCC surveillance. Ultrasonography has lower sensitivity in obese individuals. Therefore, several smaller studies have explored the use of abbreviated MRI to overcome the hurdles of cost and accessibility

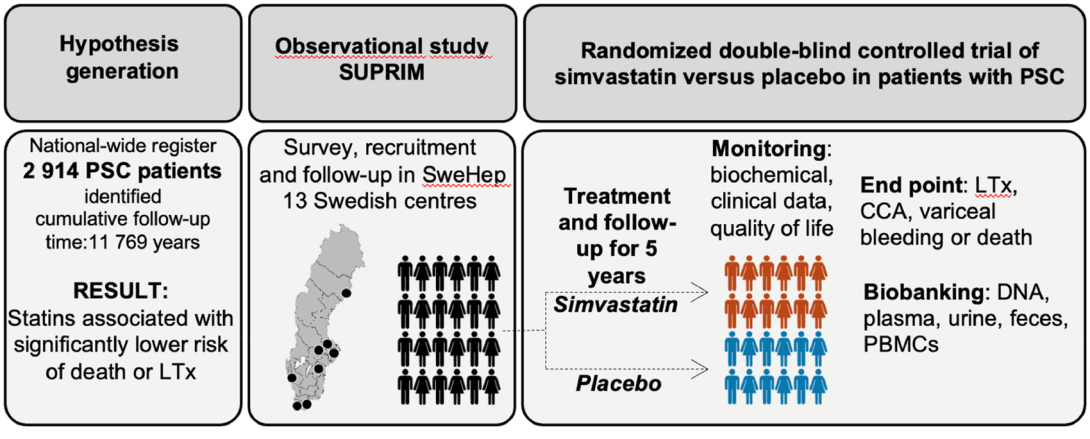

Figure 1. Overview of the PiSCATIN study.

associated with MR scans [43]. Building on the framework of a previous Swedish cirrhosis study, ACCESS-ESLD [44], we aim to conduct a head-to-head comparison of abbreviated MRI with ultrasound. In September 2024, we launched the DETECTC-ESLD study, a prospective multicenter cohort study conducted within the SWEHEP network. The study will enroll patients with liver cirrhosis at eleven Swedish hospitals and two international study sites. We plan to include 600 patients who will undergo an abbreviated MRI and ultrasound every 6 months for a total of four investigations. At each study visit, a detailed clinical examination will be performed, including the assessment of sarcopenia, Fibroscan, routine blood tests, and biobanking of DNA, serum, and plasma. The MRI protocol includes contrast-enhanced abbreviated MRI, body composition analysis, liver and spleen volume assessment, and magnetic resonance elastography. This data set will enable us to investigate blood- and imaging-based biomarkers for the full spectrum of liver-related complications. Please see Figure 2 for the study design.

The Swedish Registry for Liver Cirrhosis. The Swedish Registry for Liver Cirrhosis (SRL) is a National Quality Registry started in 2021. SRL has its origin in a research registry initiated by SILK about 20 years ago and has undergone continuous development during the years. Recently Uppsala Clinical Research Center (UCR), one of the major centers for National Clinical Quality Registries in Sweden, has taken over the administration, support, and further development of the registry.

The primary purpose of SRL is to support evidence-based treatment of liver cirrhosis and constitute the basis for quality evaluation of cirrhosis care in Sweden but will also be used in research within the framework of SWEHEP. In the registry, many variables are collected including demographics, cirrhosis aetiology, disease stage, biochemistry, type of decompensations, investigations, treatments, and medication. Up to date approximately 1500 patients have been registered in SRL.

Educational activities. The clinical research projects within SILK/SWEHEP are directly relevant for educational purposes. A need for structured learning activities in hepatology during specialist training in gastroenterology and as part of continuing professional development of specialists in gastroenterology was recognised early after the formation of SILK. The yearly meetings of the Swedish Society of Gastroenterology ('Gastrodagarna') and the Journal of the Swedish Medical Association ('Läkartidningen') were identified as particularly suitable platforms for such learning activities.

For many years, SILK/SWEHEP organised half-day hepatology symposia open for all participants at 'Gastrodagarna'. These were developed around themes relevant for every-day clinical practise. They also offered opportunities to present national research performed within SILK/SWEHEP and evoke interest in hepatology among younger participants. Representative examples of such themes, each covered during a half-day session, are 'autoimmune liver disease', 'cholestatic chronic liver disease', 'evaluation of elevated liver function tests', 'metabolic liver disease', 'veno-occlusive liver disease', 'chronic hepatitis' and 'genetic haemochromatosis'. Focus was always on pathogenesis, epidemiology, clinical presentation, diagnosis, treatment, follow-up and prognosis.

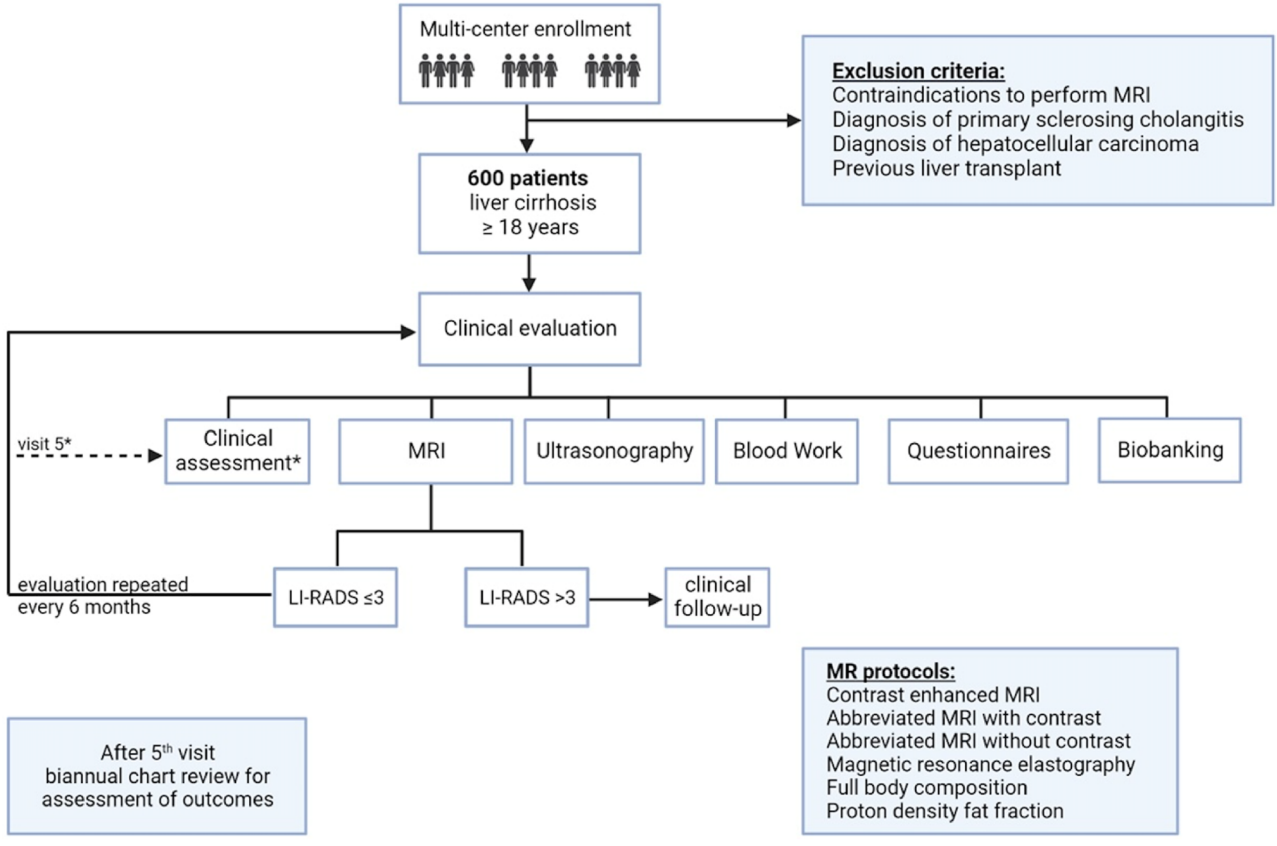

Figure 2. Study design of HCC-DETECT.

Some of these topics were also presented as a series of papers in an individual issue of 'Läkartidningen', offering an up-to-date overview of common and clinically relevant aspects of practical hepatology, based on collaborative, internationally recognised Swedish research. Several of these papers were later developed into national guidelines, published by the Swedish Society of Gastroenterology, with members of SILK/SWEHEP as main authors. The obligation to spread the results of the research activities to a broad audience and thereby improve clinical practise has always been central to SILK/SWEHEP. Still, there is a close collaboration between SWEHEP and the Swedish Society of Gastroenterology. The education in hepatology in Sweden is nowadays further developed and pursued by the section of hepatology and the section of education.

The group philosophy. The philosophy of the group has developed over the years but has always been characterized by curiosity, ambition and mutual trust. The working climate is crucial, and a lot of time and energy have been spent to get to know each other and to build and keep trust between members. There is a continuous ongoing discussion on the purpose of the group. One important goal is that all seven university hospitals are represented and at least one project is driven from each center. New ideas are always welcome. When a new project idea is proposed, it is discussed and criticized to be improved. The feasibility is investigated in the different centers between the meetings, regarding for example patient recruitment or resources. Usually, it takes 3–4 meetings (2 years) to develop the idea before decision is taken to move forward.

Funding is an obvious issue, and each center is responsible for the funding of its own research staff. When larger funds are received resources are shared. Authorship is discussed in advance. Some PhD students have been performing most of their academic studies in collaboration with the group. This ensures continuation and recruitment of new members and offers network opportunities for young researchers. The members of the group are loyal to the projects and the goal is to feel that everyone benefits from being part of the collaboration. The members have also been encouraged to be active members of interational associations such as AASLD, EASL and UEG and present the work at their scientific meetings (Table 2).

Future perspectives. SWEHEP has hitherto made a significant contribution to the field of hepatology. The educational responsibility is nowadays taken care of within the Swedish Society of Gastroenterology where many members of SWEHEP play important and active roles.

Table 2. Success factors for SILK-SWEHEP.

- Any ideas are welcome
- Members participate in all meetings
- Development of new projects are done in collaboration
- Meetings are regular and always follow-up status of ideas and projects
- Every member should at least contribute actively to at least one project
- Members who do not contribute leave the group
- The collaboration is based on trust
- We focus on few projects
- Leadership has been persistent over the years
- Social activities and having fun together are prioritized

SWEHEP will continue to explore emerging technologies and innovative research approaches to advance knowledge in diagnosing and treating liver diseases. With further adaptive clinical trial designs and real-world evidence studies our aim is to identify and validate drugs, biomarkers, and imaging techniques for treatment, early detection and monitoring of liver diseases. In the near future, comprehensive genomic profiling may identify genetic mutations and pathways involved in disease progression. Personalized treatment plans based on an individual's genetic makeup are becoming increasingly feasible, enhancing therapeutic efficacy and minimizing adverse effects.

Further studies conducted by SWEHEP will hopefully contribute significantly to this field as well and SWEHEP is prepared to contribute with a large collection of samples and data on chronic liver diseases.

Sharing data and resources across institutions and countries accelerates the pace of discovery and improves the generalizability of research findings. A prioritized future alignment of SWEHEP is to participate in collaborative international research networks and consortia, which will be essential for addressing the global burden of liver diseases.

The future of hepatology research and SWEHEP is bright. We can look forward to significant improvements in the prevention, diagnosis, and treatment of liver diseases, ultimately enhancing patient outcomes and quality of life.

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