IPSCSG PROGRAMME
9th – 10th of September 2024

Monday 9th September

11:30-12:30	**Registration. Lunch and networking**	
12:30-12:45	Welcome to Karolinska and Stockholm	Annika Bergquist
12:45-13:00	Patients´ perspective on PSC research	Martine Walmsley
13:00-14:00	**Session 1. Understanding the pathophysiology in PSC** **Chairs: Niklas Björkström; Espen Melum**	
13:00-13:15	Immunology of PSC	Niklas Björkström
13:15-13:30	Intergenic risk variant rs56258221 skews the fate of naive CD4+ T cells via miR4464-BACH2 interplay in primary sclerosing cholangitis	Tobias Poch
13:30-13:45	Studying mechanisms of primary sclerosing cholangitis in vitro using a bile duct on a chip	Henry Hoyle
13:45-14:00	Discussion and future Research Agenda	Niklas Björkström, Espen Melum
14:00-15:15	**Session 2. PSC-IBD** **Chairs: Maria Londono, Cyriel Ponsioen**	
14:00-14:15	IBD immunology – outlook towards PSC -IBD	Jenny Mjösberg
14:15-14:30	The gut-liver axis and microbiota	Johannes Hov
14:30-14:45	PSC- IBD report from the ERN PSC- IBD workshop	Nora Cazzagon
14:45-15:00	Structural and immunological markers of gut barrier injury in primary sclerosing cholangitis	David Tornai
15:00-15:15	The bidirectional regulatory network of immune cells and cholangiocytes	Nicola Iuso
15:15-15:30	Discussion and future Research Agenda	Maria Londono
15:30-16:30	**Coffee break with poster tour 1 and networking**	
16:30-17:30	**Session 3. Advances in diagnostics and prognostics – MRI/ERCP/elastography** **Chairs: Kristina Ringe; Nora Cazzagon**	
16:30-16:45	The role of MRI/ERCP for prognostication in PSC	Henrike Lenzen
16:45-17:00	Validation of the DiStrict score. A multicenter study within the iPSCSG.	Aristeidis Grigoriadis
17:00-17:15	Value of sarcopenia for prognostication in patients with PSC	Alena Levers
17:15-17:45	**New initiatives** **Chairs: Tom H Karlsen, Annika Bergquist**	
17:15-17:40	The Resnek Family Center for PSC Research	Josh Korzenik
17:40-17:50	PSC Award	Tom H Karlsen

19:00	**Dinner**	

Tuesday 10th September

08:15- 09:40	**Session 4. Cholangiocarcinoma (in PSC)** **Chairs: Niklas Björkström; Trine Folseras**	
08:20-08:40	Precision medicine in CCA diagnostics and treatment	Gregory Gores
08:40-09:00	ENSCCA activity – an overview	Jesus Banales
09:00-09:15	Bile extracellular vesicles hold protein biomarkers for the early diagnosis of cholangiocarcinoma in individuals with primary sclerosing cholangitis	Ainhoa Lapitz/Pedro Rodriges
09:15-09:30	Developing a DNA methylation-based blood test for the prognosis of PSC and early detection of biliary tract cancers	Ghada Nouairia
09:30-09:40	Discussion and future Research Agenda	Trine Folseras
09:40-10:40	**Coffee break with poster tour 2 and networking**	
10:40-12:15	**Session 5. Clinical studies** **Chairs: Annika Bergquist; Cynthia Levy**	
10:40-10:55	Utility of organoids in large scale drug screening outlook towards PSC	Volker Lauschke
10:55-11:15	Surrogate endpoints for clinical trials	David Assis
11:15-11:30	Patient reported measures in PSC research	Mette Vesterhus
11:30-11:45	Pathological Klebsiella pneumoniae determines the clinical course of primary sclerosing cholangitis and potentially serves as therapeutic targets	Nobuhiro Nakamoto
11:45-12:00	Continued Development and International Validation of the Provisional UK-PSC-QoL Tool	Ryan James
12:00-12:15	Discussion and future Research Agenda	Annika Bergquist, Cynthia Levy
12:15-13:00	**Lunch, poster viewing and networking**	
13:00-14:00	**Session 6. Improvements in surgery and transplantation for PSC** **Chairs: Gabriel Oniscu; David Assis**	
13:00-13:15	rPSC – definition, prevention and impact of IBD	Palak Trivedi
13:15-13:30	Alkaline phosphatase and clinical scores predict outcome in recurrent primary sclerosing cholangitis after liver transplantation	Lise Katrine Engesæter

13:30-13:45	Discussion and future Research Agenda	Gabriel Oniscu, David Assis
13:45-14:30	**IPSCSG steering committee**	
13:45-14:15	Re-election IPSCSG steering committee	Ansgar Lohse
14:15-14:30	Closing remarks	Annika Bergquist

Abstract Nr	Area	Abstract title
1	**Bile tract cancer**	Diagnostic Optimization in Unclear Biliary Lesions (DOUBLE) - Developing a novel diagnostic Algorithm for the Differentiation of benign and malignant biliary Strictures
2	**Bile tract cancer**	Developing a DNA methylation-based blood test for the prognosis of PSC and early detection of biliary tract cancers
3	**Bile tract cancer**	Bile extracellular vesicles hold protein biomarkers for the early diagnosis of cholangiocarcinoma in individuals with primary sclerosing cholangitis
4	**Bile tract cancer**	International Consortium for the Genetics of Biliary Tract Cancers
5	**Prognosis**	Utility of Transabdominal Elastography and Fib-4 Index in Predicting the Prognosis of Primary Sclerosing Cholangitis
6	**Prognosis**	Liver stiffness as a dynamic prognostic indicator for decompensation, transplant and death in primary sclerosing cholangitis
7	**Prognosis**	Machine-learning based multi-OMICs serum analysis from Primary Sclerosing Cholangitis reveals hallmarks associated with disease phenotypes and progression
8	**Prognosis**	Macrophage activation markers in primary sclerosing cholangitis
9	**Prognosis**	Structural and immunological markers of gut barrier injury in primary sclerosing cholangitis
10	**Prognosis**	Scandinavian PSC Biobank (ScandPSC) - A opportunity for future biomarker studies
11	**Prognosis**	Defining Acute Cholangitis as a Clinical Outcomes Endpoint in Adults with PSC: Results of a Multinational Patient Survey to Develop a Patient-Reported Outcomes Measure
12	**Prognosis**	Prevalence of steatotic liver disease (SLD) and its impact on adverse clinical outcomes in people living with primary sclerosing cholangitis (PSC)
13	**Imaging/ERCP**	Validation of the DiStrict score. A multicenter study within the iPSCSG.
14	**Imaging/ERCP**	Value of sarcopenia for prognostication in patients with PSC
15	**Imaging/ERCP**	Usefulness of peroral cholangioscopy (POCS) in the diagnosis and follow-up of PSC
16	**Imaging/ERCP**	The early dynamic changes of radiological and biochemical scores help identify a more aggressive PSC phenotype

17	**Imaging/ERCP**	The protective role of gallbladder presence and enlargement in patients with Primary Sclerosing Cholangitis: preliminary analysis of a multicentric study
18	**Imaging/ERCP**	Complications of ERCP and sphincterotomy in primary sclerosing cholangitis
19	**Pathogenesis**	Genome-scale autoantibody profiling in primary sclerosing cholangitis provides an ATLAS of autoimmune traits associated with clinical phenotypes and disease progression
20	**Pathogenesis**	The role of interleukin-8 in primary sclerosing cholangitis-associated immune cell dysregulation
21	**Pathogenesis**	Assessing the Gut Barrier Dysfunction in Pediatric Sclerosing Cholangitis through a Metagenomic and Metabolomic analysis of Mucosal Microbiome (MuMi Study)
22	**Pathogenesis**	Intergenic risk variant rs56258221 skews the fate of naive CD4+ T cells via miR4464-BACH2 interplay in primary sclerosing cholangitis
23	**Pathogenesis**	Distinct gene pathways and cell types define peribiliary disease states in PSC
24	**Pathogenesis**	Enterococcus faecalis virulence determines intestinal barrier translocation in murine sclerosing cholangitis
25	**Pathogenesis**	Pathological Klebsiella pneumoniae determines the clinical course of primary sclerosing cholangitis and potentially serves as therapeutic targets.
26	**Pathogenesis**	Studying mechanisms of primary sclerosing cholangitis *in vitro* using a bile duct on a chip
27	**Pathogenesis**	Single-cell sequencing of PSC patient liver tissue identifies an altered immune landscape and characterizes epithelial and stromal responses
28	**Pathogenesis**	Tissue resident natural killer (NK) cells in the human biliary tract system
29	**Pathogenesis**	Single-nuclei sequencing of human liver samples reveals heterogeneity and compositional changes of biliary epithelial cell subpopulations during the progression of primary sclerosing cholangitis
30	**Pathogenesis**	THE CONCENTRATIONS OF TNFRSF14 AND LIGHT IN THE SERA AND BILE OF THE PATIENTS WITH PRIMARY SCLRELOSING CHOLANGITIS
31	**PSC-IBD**	PSC-IBD with IBD as a Comparator: Epidemiological Patterns in Incidence, Prevalence, and Outcomes at the Population Level
32	**PSC-IBD**	Dietary Practices and Beliefs in Individuals with Primary Sclerosing Cholangitis
33	**PSC-IBD**	The bidirectional regulatory network of immune cells and cholangiocytes

34	**PSC-IBD**	Safety and Efficacy of Upadacitinib in patients with PSC-IBD
35	**rPSC/LTX**	Alkaline phosphatase and clinical scores predict outcome in recurrent primary sclerosing cholangitis after liver transplantation
36	**rPSC/LTX**	Serological markers of intestinal barrier function in patients with primary sclerosing cholangitis and inflammatory bowel disease after liver transplantation
37	**Surveillance**	The Swedish initiative for the study of Primary sclerosing cholangitis (SUPRIM)
38	**Surveillance**	Gallbladder polyps in PSC and rates of malignancy: time for a multicentre study?
39	**Surveillance**	The long-term variability of pruritus in primary sclerosing cholangitis: results of an observational cohort study
40	**Surveillance**	A Protocol for the Development of a Core Outcome Set for Clinical Trials in PSC
41	**Surveillance**	Continued Development and International Validation of the Provisional UK-PSC-QoL Tool

Deadline is May 15th, 2024. Write "Proposal for IPSCSG meeting" in the subject line. Send it to annika.roback@regionstockholm.se

Title of Abstract

1. Diagnostic Optimization in Unclear Biliary Lesions (DOUBLE) - Developing a novel diagnostic Algorithm for the Differentiation of benign and malignant biliary Strictures

Authors; Name, title (Mark presenting author with *) and Institution (s)
*Jan Philipp Weltzsch, MD, I. Dept. of Medicine, University Medical Centre Hamburg-Eppendorf
Jenny Krause, MD, I. Dept. of Medicine, University Medical Centre Hamburg-Eppendorf
Christoph Schramm, MD, I. Dept. of Medicine, University Medical Centre Hamburg-Eppendorf

Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background: People with initially undetermined biliary strictures, particularly those with primary sclerosing cholangitis (PSC), face a high risk of developing cholangiocarcinoma (CCA). The differentiation between fibrotic / benign and malignant strictures is challenging, which often delays therapy initiation in case of an ultimately malignant finding. Recently, new methods were developed to improve the diagnosis of CCA, such as liquid biopsy approaches and proteomics. The development of an accurate diagnostic algorithm incorporating conventional and novel methods for the early detection of CCA is of high clinical relevance and represents an unmet clinical need, particularly in people with PSC.

Hypothesis: A prospective analysis of biomarkers, including epigenetic markers, proteomic profiles, extracellular vesicles (EV), miRNA and cell-free DNA (cfDNA), will allow for the development of a diagnostic algorithm which is superior to current clinical standards in detecting CCA.

Methods: Since 04/2022, we have collected clinical data and biosamples from >75 people with initially undetermined biliary strictures, including 54 patients with PSC and 11 with confirmed malignancy. Epigenetic promotor analyses, as well as analyses of cfDNA (quantification, mutation profiling), EV and serum/urine proteomics will be conducted. Fluorescence in-situ hybridization of biliary brushings has been implemented as the clinical standard within the study's preliminary work. EV/miRNA analyses (characterization, miRNA analyses, proteomics) have already been established, as have been international collaborations for the proteomics analyses. We will assess individual diagnostic parameters for their accuracy in detecting CCA, followed by model comparisons using traditional statistical and machine learning approaches.

Aims: To develop a combinatorial diagnostic algorithm that is superior to standard of care by reducing the time to diagnosis and the number of invasive procedures needed to establish a definite diagnosis.

Conclusions: We here present the ongoing DOUBLE study for potential future collaboration in a prospective multicentre validation study.

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Biomarkers for bile tract cancer

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Title of Abstract

2. Developing a DNA methylation-based blood test for the prognosis of PSC and early detection of biliary tract cancers

Authors; Name, title (Mark presenting author with *) and Institution (s)
Ghada Nouairia*, PhD, Department of Medicine Huddinge, Karolinska Institutet, Sweden
Martin Cornillet, PhD, Center for Infectious Medicine, Karolinska Institutet, Sweden
Annika Bergquist, MD, PhD, Professor, Department of Medicine Huddinge, Division of Hepatology, Karolinska Institutet , Karolinska University Hospital, Sweden

Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Primary sclerosing cholangitis (PSC) is the most established risk factor for the development of biliary tract cancers (BTC); cholangiocarcinoma (CCA) and gallbladder cancer (GBC). These tumours are rare and often diagnosed at a late stage leading to poor survival. There are currently no efficient tools for the diagnosis, prognosis, and monitoring of BTC development in PSC. The pathogenesis of both BTC and PSC are poorly understood, limiting the development of therapeutic tools. As epigenetic mechanisms, such as DNA methylation, are now recognized as a hallmark of cancer and constitute a dynamic process throughout the human lifetime, we hypothesize that disease-related DNA methylation alterations are detectable in the peripheral blood of patients. We aim to identify such alterations in the peripheral blood that (1) behold prognosis potential to predict severe outcomes of PSC and (2) detect BTC at an early stage. The study is also designed to unveil specific methylation signatures of BTCs and PSC to provide new biological insights.

Methods

DNA was purified from the whole blood of 110 individuals: CCA (40), GBC (21), PSC (19) and PSC with BTC (10) and healthy donors (20). We used the largest currently available DNA methylation profiling array, Illumina Infinium EPIC beadchip on 850 000 sites across the genome, at the Bioinformatics and Expression Analysis (BEA) core facility at KI, Campus Flemingsberg. We also collected clinical data of the patients including the outcomes (overall survival for cancer patients, liver transplantation, BTC re-occurrence or death in PSC patients). We have a follow-up of at least 3 years after surgery for GBC and CCA patients and up to 13 years after sampling for individuals with PSC without cancer.

Results

We describe the first genome-scale DNA methylation profiles of BTC and reveal significant differentially methylated sites and regions related to CCA, GBC, and PSC as compared to healthy individuals. Using machine learning methods, we identify several combinations of informative methylation sites with reliable diagnosis potential for CCA and GBC. Using clinical follow-up data on the CCA and GBC patients, we identified several markers that can, when combined, predict the outcome of surgical resection of the tumour in term of 18 months survival with high specificity and sensitivity.
Using enrichment analysis, we identified genes and pathways potentially involved in these biliary disorders, with some known to have a role in cancer and that might have implications for disease monitoring.

Conclusion

We provide genome-scale DNA methylation profiles of biliary tract cancers and PSC. We identify DNA methylation sites and genome regions with diagnosis and prognosis potential of BTC in high-risk populations.

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Biomarkers for bile tract cancer

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Title of Abstract

3. Bile extracellular vesicles hold protein biomarkers for the early diagnosis of cholangiocarcinoma in individuals with primary sclerosing cholangitis

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Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background and Aims: Cholangiocarcinoma (CCA) presents a significant threat to individuals with primary sclerosing cholangitis (PSC), with a 20-year cumulative incidence of approximately 15%. Early diagnosis is challenging due to overlapping symptoms, and recommended MRI/MRCP surveillance every 6-12 months often proves suboptimal in detecting early-stage cancer. PSC-CCA patients face a dismal prognosis, with a median overall survival of 5-12 months in unresectable cases, making CCA the primary cause of PSC-associated mortality. There is a critical need for more accurate early detection methods, allowing access to potentially curative options like tumor resection or liver transplantation. In this regard, investigating extracellular vesicles (EVs) in bile, which come into direct contact with CCA tumors, offers a promising avenue for identifying diagnostic CCA biomarkers in PSC, and these were evaluated in this study.
Method: Bile EVs were collected from patients with isolated PSC (PSC, n=52), PSC with CCA (PSCCCA, n=14), or PSC at time of sampling but who later developed CCA (PSC to CCA, n=8), at Oslo University Hospital Rikshospitalet (Norway). The EV-protein content was characterized using mass spectrometry. Diagnostic biomarkers for PSC-CCA, as well as early-diagnostic/predictive biomarkers for the PSC to CCA group were identified and combined using binary logistic regression multivariable models.
Results: High-throughput proteomics of bile EVs identified 21 diagnostic biomarkers for PSC-CCA, regardless of sex, age, the presence of inflammatory bowel disease, or cirrhosis at the time of sampling. Among these, 14 biomarkers were observed to be more abundant, and 7 exhibited lower levels in patients with PSC-CCA compared to patients with isolated PSC. Machine learning algorithms revealed COPA/ATP5H/VTNC/IQGA1/PRDX2 (AUC=0.996) and COPA/ATP5H/VTNC/IQGA1/CALX/PRDX2 (AUC=1.000) as highly effective in diagnosing PSC-CCA versus isolated PSC, surpassing the performance of serum CA19-9 alone (AUC=0.846). Notably, the logistic model combining TM9S4/RS18/LPPRC/NHRF1 demonstrated predictive capacity for CCA development in PSC before any clinical evidence of malignancy with 100% sensitivity and specificity (AUC=1.000), whereas serum CA19-9 exhibited no significant predictive capacity for CCA development (AUC=0.596).

Conclusion: Bile EVs harbor valuable protein biomarkers for predicting the development of CCA and enabling early diagnosis in individuals with PSC. Given the ease of bile collection during stenting for dominant strictures in individuals with PSC, this innovative liquid biopsy tool may be of significant value for monitoring disease progression and aiding access of potentially curative treatment options.

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Biomarkers for bile tract cancer

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Title of Abstract

4. International Consortium for the Genetics of Biliary Tract Cancers

Authors; Name, title (Mark presenting author with *) and Institution (s)
Caitlin VanLith* (MD/PhD Student, Mayo Clinic), Younghun Han (Baylor College of Medicine), Matthew Cooley (Mayo Clinic), Chris Amos (Professor, Baylor College of Medicine), Manal Hassan (MD Anderson), Katherine McGlynn (US NCI), Lewis Roberts (Mayo Clinic)

Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Increasingly, germline genetic contributions to cholangiocarcinoma (CCA) development are being recognized. The International Consortium for the Genetics of Biliary Tract Cancers is an extensive global network of hepatobiliary researchers and physicians, and, as the consortium's first major project, we are conducting a large genome-wide association study (GWAS) and epidemiological exploration of cholangiocarcinoma. As part of a discovery phase of the GWAS, germline DNA of 2,366 persons with CCA (891 iCCA, 1,041 eCCA, 2,179 non-primary sclerosing cholangitis [PSC]-related CCA, and 187 PSC-related CCA) and 11,750 persons without CCA in populations of European ancestry was sequenced using the Illumina Global Screening Array. Two novel variants were found at the genome-wide significance level ($p<5E-8$) for eCCA and non-PSC-related CCA: LINC02506 on 4p15.1 (OR=0.17, P=3.20×10-8) for eCCA and THSD7A on 7p21.3 (OR=2.98, P=4.94×10-9) for non-PSC-related CCA. In addition, 10 variants were found at a suggestive level ($p<5E-7$), including on 15q25.3 (AGBL1) for PSC-related CCA. These preliminary results warrant a large expansion phase of the GWAS, which we are currently undertaking. Our goal is to sequence 7,000 CCA cases and 14,000 controls from all global regions over the next four years in order to compile the largest genetic study of CCA to date. An important subanalysis of this project is the distinction between PSC-related CCA and non-PSC-related CCA, as we hypothesize that the genetic predispositions between these cases will be different. We are hoping that members of the International PSC Study Group will partner with us in this investigation to better understand the germline genetics behind CCA and the progression of PSC to CCA. Recognition of biomarkers that predispose individuals to CCA development are necessary in understanding pathogenesis and developing better diagnostics and targeted therapy, ultimately increasing quality of life and survival in these patients.

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Biomarkers for bile tract cancer

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Title of Abstract

5. Utility of Transabdominal Elastography and Fib-4 Index in Predicting the Prognosis of Primary Sclerosing Cholangitis

Authors; Name, title (Mark presenting author with *) and Institution (s)
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Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Objective: Primary sclerosing cholangitis (PSC) is a chronic progressive liver disease with bile stasis that can progress to decompensated cirrhosis and is associated with cholangiocarcinoma, a challenging condition to treat. Although the exact pathogenesis is unclear, it is expected that liver fibrosis progresses due to bile stasis and recurrent cholangitis, leading to cirrhosis. This study focuses on markers of liver fibrosis to examine their correlation with patient background and disease duration, and to assess their potential for prognosis prediction.

Methods: The study included patients diagnosed with PSC from April 2000 to August 2022. Markers of liver fibrosis used were the Fib-4 index and liver stiffness measurements (kPa) obtained via transabdominal elastography (EG). The progression of fibrosis markers was calculated as the difference between the initial and the most recent values at our hospital, and as the slope of the curve approximating this progression. The correlation between the progression of fibrosis markers, patient background, disease duration, and observation period at our hospital was analyzed.

Results: The study involved 31 cases (14 males) diagnosed with PSC and followed up at our hospital. The median disease and observation periods were 72 months (range 1-247 months) and 33 months (range 1-220 months), respectively. Two cases were complicated by cholangiocarcinoma. Longer disease duration significantly correlated with higher recent Fib-4 index ($p=0.019$) and liver stiffness values ($p=0.008$). Longer observation periods at our hospital were significantly associated with a steeper slope of Fib-4 index changes and approximation curve ($p=0.004$). Cases with cholangiocarcinoma had a significantly steeper slope of Fib-4 index (0.0100 vs 0.0002; $p=0.009$) compared to those without malignancy.

Discussion: Fib-4 index and EG liver stiffness measurements are useful indicators of the progression of liver fibrosis in PSC, and their temporal progression can predict future fibrosis advancement. A steep slope in the Fib-4 index approximation curve should warrant caution for potential cholangiocarcinoma. Future challenges include accumulating more cases and integrating the clinical progression and prognosis prediction with conditions such as obstructive jaundice and cholangitis.

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Biomarkers for prognosis

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Title of Abstract

6. Liver stiffness as a dynamic prognostic indicator for decompensation, transplant and death in primary sclerosing cholangitis

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Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background/Aims: Liver stiffness measurement (LSM) by transient elastography (TE) has been found to be strongly associated with fibrosis stages in primary sclerosing cholangitis (PSC), with cutoffs of <9.7 kPa, 9.4-14.4 kPa, and >14.4 kPa corresponding to F1/F2, F3, and F4 respectively1. As such, LSM has the potential to be a useful prognostic indicator that can be assessed dynamically over time.

Methods: In a retrospective cohort of individuals with PSC followed at a single tertiary care liver clinic from 2000-2020 who underwent TE prior to liver transplant, the relationship between LSM readings at baseline and readings to progression to a composite of decompensation (ascites, variceal hemorrhage, hepatic encephalopathy), transplant, or death were assessed using 2 regression methods: Cox proportional hazards with time-dependent variables and joint modelling. Covariates evaluated included age, sex, biochemistry (bilirubin, ALP, albumin, platelets within 30 days of LSM reading), PSC duration, and inflammatory bowel disease (IBD) duration. The effect of DLSM with a 2-year lookback period was also evaluated with joint modelling.

Results: Individuals who underwent TE had median age 35 y.o. (IQR 25-49), were 61% male, and 75% had concurrent IBD. Two-thirds of the cohort had 2+ TE readings. There were 65 decompensating events, 23 liver transplants and 20 deaths overall; after excluding TE readings done after decompensating events, there were 826 readings from 375 individuals with 46 composite events. On univariate analysis, per 1 log increase in TE reading, there was a 3.7-fold increase in risk of decompensation, transplant, or death (95%CI 2.64-5.18). With multivariable time-dependent Cox regression accounting for age, sex, ALP, and total bilirubin, TE reading remained predictive of outcome (HR 2.55, 95%CI 1.62-4.00). This did not fluctuate significantly with addition of platelets & albumin or IBD duration & PSC duration in the model. Stratification by fibrosis level demonstrated a HR of 2.49 (95%CI 0.99-7.02) for TE readings 9.7-14.4 kPa, and HR of 4.57 (95%CI 1.94-10.8) for readings >14.4 kPa while accounting for age, sex, bilirubin, and ALP. By itself, risk of decompensation/transplant death increases by an HR 1.70 (95% CI 1.26-3.53) per unit DLSM(kPa)/year; stability of LSM corresponded to stable outcome risk.

Conclusion: This retrospective study validates evidence for LSM as a longitudinal prognostic tool for clinically meaningful outcomes in PSC, as well as substantiates cutoffs for risk stratification, a key component of clinical prognostication and future therapeutic trials.

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Biomarkers for prognosis

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Title of Abstract

7. Machine-learning based multi-OMICs serum analysis from Primary Sclerosing Cholangitis reveals hallmarks associated with disease phenotypes and progression

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Annika Bergquist, MD, PhD, Professor, Department of Medicine Huddinge, Division of Hepatology, Karolinska Institutet , Karolinska University Hospital, Sweden

Body text (background/rational, methods, preliminary results, what you ask for- your proposal)
Background
Primary sclerosing cholangitis clinical phenotypes and progression are heterogenous and unpredictable. These can be delignated based on the presence or absence of inflammatory bowel disease (IBD), end stage fibrotic disease or cholangiocarcinoma (CCA). The biological mechanisms driving those are poorly understood and better markers are needed to anticipate disease progression. Although the liver and the biliary tract are the prominent sites of disease manifestations, a large amount of blood is passing the liver, where the damaged tissue might release fingerprint of the local pathophysiology. Therefore, we hypothesize that a deep characterization of the peripheral circulation can capture biological disturbance hallmarks of the clinical phenotypes.

Methods
We first performed a deep circulome characterization by quantifying serum proteomics (1000 proteins), metabolomics (1000 metabolites), and miRNA sequencing (2600 sequences) from 36 PSC patients representing 5 distinct prototypical phenotypes and stages of the disease, as well as healthy donors as a reference. PSC phenotypes were defined a PSC with CCA (n = 6), PSC without IBD (n = 8), fast progressing to the need for liver transplantation (less than 10 years, n = 6), and early (n = 6) or advanced (n = 7) based on the fibrosis level.

We used machine learning methods such as Lasso regression and elastic net to identify biological features characteristics of each phenotype and integrated this data to build a multimodal network of PSC subtypes inferring biological progressions patterns.

Results
We identify tentative hallmarks of different PSC phenotypes; individuals with and without IBD, those progressing faster toward end stage liver disease, and those with CCA. In addition, we generated biological networks revealing pathological pathways associated with these phenotypes. These findings provide mechanistic insights into distinct PSC subtypes that might have implications for further research including disease models, personalized management plans, and targeted therapy.

Conclusion/Summary
In this proof-of-concept study, we show that biological patterns mirroring PSC phenotypes and progression are detectable in the serum from patients. Although further validations are required involving larger cohorts, this might offer opportunity to monitor disease progression non-invasively, and applications for early cancer detection, and assessing drug response.

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Biomarkers for prognosis

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Title of Abstract

8. Macrophage activation markers in primary sclerosing cholangitis

Authors; Name, title (Mark presenting author with *) and Institution (s)
Bence Toth,MD*; David Tornai,MD,PhD; Maria Papp,MD,PhD,DSc
Department of Internal Medicine, Division of Gastroenterology, Faculty of Medicine, University of Debrecen

Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background and Aims:
Macrophages and monocytes are significant contributors to the progression of primary sclerosing cholangitis (PSC) through their involvement in perpetuating inflammation, immune dysregulation, and promotion of fibrosis. Previous studies reported elevated serum levels of macrophage activation markers in PSC but data on their significance is scare.
Methods:
We have measured serum level of 4 macrophage/monocyte markers (sCD163, sCD206, sCD14 and suPAR) in 93 patients with PSC. Patients were followed for 10 years and association between markers and inflammatory bowel disease (IBD), cirrhosis, and outcome have been investigated.
Results:
Levels of all macrophage markers were correlated with cholestasis (bilirubin, γ-glutamyl transpeptidase, alkaline phosphatase) and except for sCD206, also with aspartate aminotransferase and alanine aminotransferase. All markers were increased in patients with cirrhosis ($p<0.001$; 0.008; 0.016; <0.001, respectively) but not affected by concomitant IBD. Increased levels of sCD163, sCD14 and suPAR were associated with worst transplant free survival within 10 years (AUROC: 0.798; 0.731; 0.848 respectively; $p<0.001$ for all).
Conclusion:
Macrophage activation markers seem to be promising markers of progressive disease course of PSC. We would like to investigate the association between levels of these markers and non-invasive markers of liver fibrosis and portal hypertension (FIB4, liver and spleen stiffness measurements) consecutively in newly diagnosed patients.

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Biomarkers for prognosis

Deadline is May 15th, 2024. Write "Proposal for IPSCSG meeting" in the subject line. Send it to annika.roback@regionstockholm.se

Title of Abstract

9. Structural and immunological markers of gut barrier injury in primary sclerosing cholangitis

Authors; Name, title (Mark presenting author with *) and Institution (s)
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Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background and Aims:
The gut-liver axis is a key driver of the pathogenesis of primary sclerosing cholangitis (PSC). In our previous research, we found serum level of villin-1, a structural protein in the epithelial brush border, and secretory (s)IgA to be associated with gut barrier injury/dysfunction in acutely decompensated cirrhosis. In this study, we investigated the significance of these markers in PSC.
Methods:
We have measured serum level of sIgA and villin-1 in 93 patients with PSC. Patients were followed for 10 years and association between markers and inflammatory bowel disease (IBD), cirrhosis, and outcome have been investigated.
Results:
Levels of villin-1 were correlated with γ-glutamyl transpeptidase. Levels of sIgA were correlated with all liver enzymes, bilirubin, and albumin and macrophage activation markers. Increased villin-1 level were associated with concomitant IBD (median: 8.7 vs 14.4 ng/mL p=0.005). Serum sIgA levels were increased in the presence of cirrhosis (median 9.9 vs. 30.2 µg/mL p=0.007). Increased levels of sIgA were associated with worst transplant free survival within 10 years (AUROC: 0.783; p<0.001).
Conclusion:
Serum level of sIgA seems to be a promising marker of progressive disease course in PSC. The correlation of sIgA and macrophage markers suggests a role for bacterial translocation/gut permeability in the return of sIgA antibodies to the circulation.

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Biomarkers for prognosis

Deadline is May 15th, 2024. Write "Proposal for IPSCSG meeting" in the subject line. Send it to annika.roback@regionstockholm.se

Title of Abstract

10. **Scandinavian PSC Biobank (ScandPSC) - A opportunity for future biomarker studies**

Authors; Name, title (Mark presenting author with *) and Institution (s)
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Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background and aim

ScandPSC merges two strong research environments in Norway and Sweden in a collaborate effort to collect a large prospective biological and clinical sample collection. In Scandinavia, a relatively high incidence of PSC combined with high willingness among people with PSC to participate in research studies, limited loss to follow-up and good national registries, provide ideal conditions for high-quality, well-powered prospective studies.

Methods

People with PSC are recruited at time of diagnosis or on regular clinical visits for PSC. Clinical, biochemical and radiological variables on PSC, inflammatory bowel disease, complications, disease progression are collected in line with what is collected in the international PSC Registry (iPSCR) and ERN Rare-Liver PSC Registry. Samples (serum, EDTA blood and fecal samples) are collected yearly from 2020 and onwards. The project is ethically approved and is funded by a generous donation from the Halloran Family Foundation.

Preliminary results

By 14th May 2024, 1305 people with PSC, 690 from 21 Norwegian centres, and 615 from 11 Swedish centres have been included in the biobank. The participants demonstrate typical demographic characteristics with a male predominance, median age of about 37 years at inclusion and a concomitant IBD in approximately 80%. About 10% have PSC- AIH and 30% another autoimmune disease than IBD. The following centres are currently recruting people with PSC:

Akershus universitetssykehus KK Jørgensen, Sørlandet Sykehus, Arendal G Nordaberg, Diakonhjemmet sykehus R Cetinkaya, Sykehuset Innlandet, Elverum CM Ystrøm, Sykehuset Innlandet Gjøvik S Vatn, Sykehuset Innlandet Hamar JA Skjold, Haraldsplass Diakonale Sykehus M N Vesterhus, Sykehuset Østfold, Kalnes R O Barreto Rios, Sørlandet sykehus, Kristiansand H Wiig, Kristiansund sjukehus E Melsom, Sykehuset LevangerE Ness-Jensen, Sykehuset Innlandet Lillehammer T Søberg, Lovisenberg diakonale sykehus H Lannerstedt, , Oslo universitetssykehus Rikshospitalet T Folseraas, St.Olavs hospital HF K Aasarød, Stavanger Universitetssykehus LN Karlsen, Sykehuset i Vestfold Ø Rose, Oslo universitetssykehus, Ullevål H Midgard, Universitetssykehuset Nord- Norge H Kileng, Bærum Sykehus I Sohail, Ålesund sjukehus GAR Bergmaier.
Karolinska Universitetssjukhuset Huddinge L Lindström, Karolinska Universitetssjukhuset C Hedin, Uppsala Akademiska sjukhus, F Rorsman, Skånes unniversitetssjukhus E Nilsson, Danderyds sjukhus, A Haeggström, Sahlgrenska Universitetssjukhuset A Molinaro, Universitetssjukhuset Linköping S Kechagias, Universitetssjukhuset Örebro N Nyhlin, Norrlands Universitetssjukhus M Werner, Centralsjukhuset Karlstad Imante Lasyte.

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Select which of the following topics your abstract belongs to: Biomarkers for prognosis

Deadline is May 15th, 2024. Write "Proposal for IPSCSG meeting" in the subject line. Send it to annika.roback@regionstockholm.se

Title of Abstract

11. Defining Acute Cholangitis as a Clinical Outcomes Endpoint in Adults with PSC: Results of a Multinational Patient Survey to Develop a Patient-Reported Outcomes Measure

Authors; Name, title (Mark presenting author with *) and Institution (s)
Stephen Rossi PharmD*- PSC Partners, Martine Walmsley - PSC Support, Brian Thorsen - PSC Partners, Joanne Hatchett - PSC Partners, Donna Evon PhD - Univ. of North Carolina, Bryce Reeve - Duke Univ., Rachel Gomel - PSC Partners, Mary Vyas - PSC Partners, Ricky Safer - PSC Partners, Michael Trauner MD - Medical Univ. Vienna

Body text (background/rational, methods, preliminary results, what you ask for- your proposal)
Background: Acute cholangitis (AC) is a clinically significant, poorly understood PSC complication challenged by the lack of standardized diagnostic and treatment criteria. We report the results of a multinational patient survey to characterize the patient experience during AC to develop a patient-centered PROM for use in clinical trials and patient care.

Methods: A detailed anonymized patient survey was developed by PSC Partners and PSC Support patient organizations. Adults diagnosed with PSC and >1 cholangitis attack were invited to complete the survey. Relevant medical and AC history, symptoms, and medical interventions were collected. A visual abdominal pain locator was used to further characterize AC pain.

Results: A total of 355 of 428 responses met screening criteria. Timing of first AC attack relative to PSC diagnosis ranged from before (38%), concurrent (14%) and after (48%). Over 65% had AC in the past year with 45% having >2 attacks. Fatigue (92%) and liver pain (86%) were reported most frequently, with fatigue having highest severity during AC. Severity improved for all symptoms after AC, except anxiety. Improvements were greatest with fever/chills (55%), anorexia (51%) and liver pain (51%). Complete symptom resolution was highest for vomiting (50%) and fever/chills (46%). More patients reported no change in symptom severity after AC, with the least change seen with jaundice, brain fog and pruritus. Fatigue was the most reported new-onset symptom at 33%. Abdominal pain was most frequently located in the right upper quadrant (RUQ) during AC, independent of IBD, cirrhosis or transplant. Other reported pain locations >10% were body (73%), back (17%) and shoulder (10%). The majority of IBD patients (70%) clearly differentiated AC symptoms from IBD flares. Medical care was sought by 76%, of which 86% took oral and/or IV antibiotics. Other procedures included MRI (68%), ultrasound (57%), ERCP (44%) and stent/balloon dilation (26%). Despite AC treatment and/or resolution, 32% did not return to their perceived baseline health status, reporting persistent or new onset fatigue (44%), RUQ pain (15%) and brain fog (11%).

Conclusions: This detailed survey demonstrates a broad dynamic range of the frequency and severity of symptoms with AC. Fatigue and anxiety are under-recognized symptoms and warrant further study. No single symptom provides adequate specificity or sensitivity for AC, supporting the significant need to develop a multi-symptom PROM for both diagnosis and monitoring of AC.

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Biomarkers for prognosis

12. Prevalence of steatotic liver disease (SLD) and its impact on adverse clinical outcomes in people living with primary sclerosing cholangitis (PSC)

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Montano-Loza, Aldo J. MD, MSc, PhD

Introduction

Steatotic liver disease (SLD) is highly prevalent nowadays with up to 30% of the general population affected worldwide, thus making coexistence with other liver diseases inevitable. Primary sclerosing cholangitis (PSC) is an autoimmune liver disease characterized by stricturing of intra- and extrahepatic bile ducts, progressive liver fibrosis and a high risk of biliary malignancies, with liver transplantation (LT) being currently the only curative option. Non-invasive and point-of-care techniques, such as vibration-controlled transient elastography (VCTE), assess the degree of hepatic fibrosis (by liver stiffness measurement, LSM) and hepatic steatosis (by controlled attenuation parameter, CAP). The impact of concomitant SLD on adverse clinical outcomes in patients with PSC is unclear, especially in light of the newly introduced nomenclature. Moreover, data on the utility of CAP and its changes over time (delta-CAP) in PSC are scarce and inconclusive, warranting exploration.

Aims

1. Establish the prevalence of SLD among people with PSC.
2. Establish the frequency of subcategories of SLD (MASLD, MASH, MetALD) in people living with PSC.
3. Determine the association between concomitant SLD and adverse liver outcomes in PSC and quantify the magnitude of these associations.
4. Investigate the association and the prognostic significance of the baseline CAP and delta-CAP by VCTE in predicting adverse liver outcomes in PSC.
5. Determine if adding CAP improves the predictive value of pre-established risk estimate tools (LSM by VCTE, PREsTo and Mayo PSC risk score).

Study design

An observational, multicentre, international, retro- and prospective cohort study. We will collect data on clinical course, comorbidities, weight status, biochemistry, VCTE, diagnostic imaging, and outcomes. Diagnosis of SLD will be established by any of the diagnostic modalities (VCTE (CAP≥233 dB/min), biopsy, ultrasound, MRI, CT, etc.). Diagnosis of MASLD (metabolic-associated steatotic liver disease) will be established if the SLD co-exists with the presence of at least one

cardio-metabolic criteria (based on elevated body mass index, blood pressure, and abnormalities in glycemic and lipid profiles). Diagnosis of MetALD (metabolic-associated steatotic liver disease) will be established in the setting of MASLD and consumption of greater amounts of alcohol (140-350 g/week for females and 210-420 g/week for males). Metabolic dysfunction-associated steatohepatitis (MASH) will be established in the presence of SLD and hepatic inflammation. Adverse liver outcomes will be defined as progression of fibrosis, development of cirrhosis or liver decompensation, development of biliary malignancies, need for LT, and liver-related and all-cause death.

Inclusion criteria

- Age ≥18 y.o., both sexes
- Diagnosis of PSC, established by any of the diagnostic modalities

Exclusion criteria

- Concomitant liver diseases (autoimmune hepatitis, viral hepatitis, vascular liver disorders, hereditary syndromes, etc.)
- History of LT(s)

Sample size determination

The sample size is determined to ensure it is adequate to estimate parameters with sufficient precision. Assuming an absolute difference in risk of developing adverse liver outcomes of 5%, the sample size of n=208 will be enough for 95% CI +/-5% CI width. However, we will aim for a larger sample size of at least 1,000 people with PSC.

Topic = Biomarkers for prognosis

Deadline is May 15th, 2024. Write "Proposal for IPSCSG meeting" in the subject line. Send it to annika.roback@regionstockholm.se

Title of Abstract

13. Validation of the DiStrict score. A multicenter study within the iPSCSG.

Authors; Name, title (Mark presenting author with *) and Institution (s)
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Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background: The DiStrict score (1) is reproducible with high inter-reader agreement and is associated with liver transplantation and liver-related death. However, it has not been validated in external cohorts.
Aims: To validate the inter-reader agreement of the DiStrict score and its association with transplant-free survival in a large external multicenter international cohort.
Materials and methods: This is a retrospective multicenter international study with the participation of nine centers, all members of iPSCSG (see detailed list below). Hepatologists from each center will retrieve retrospective data of at least 50 consecutive adult individuals with PSC (MRCP, demographic data, liver tests, date of PSC diagnosis, CCA diagnosis, liver transplantation, death, and cause of death). We aim to include approximately 450 patients with at least 5 years of follow-up time according to our power calculation. After a short introduction and online education on the application of the DiStrict score, two radiologists from each center will apply the DiStrict score independently to the MRI/MRCPs of their patients. For survival analysis purposes, cases of disagreement will be resolved in consensus. Inter-reader agreement for the application of the DiStrict score will be assessed separately for each pair of radiologists from all centers with the intraclass correlation coefficient (ICC), with a two-way random effects model, absolute agreement, and single measurement. The association of the DiStrict score with transplant-free survival will be assessed in the combined cohort (n≡approximately 450) with Cox proportional-hazards regression analysis, and survival estimates will be calculated with Kaplan-Meier curves, and the curves will be compared with the log-rank test.
Preliminary results: Preliminary data from one reader from Stockholm confirm that patients with high DiStrict scores (5–8) have a higher risk of developing outcomes compared to patients with low scores (1–4) (HR≡4.29; p≡0.031). Data from two readers from Oslo-Bergen confirm the good inter-reader agreement of the score (ICC≡0.776).
Participating centers, hepatologists, and radiologists:
Yale: D.Assis (hepatologist), C.Singh (radiologist), S.Czerniak (radiologist).
Barcelona: M.C.Londono (hepatologist), S.Rodriguez(radiologist), G.Raffart (radiologist).
Amsterdam: C.Ponsioen-T.Middelburgh (hepatologists), K.Horsthuis (radiologist), J.Reimerink (radiologist).
Birmingham: P.Trivedi (hepatologist), A.Pallan (radiologist), J.Plowright (radiologist)
Hannover: H.Lenzen (hepatologist), K.Ringe (radiologist), T.Kaireit (radiologist).
Milan: L.Cristoferi (hepatologist), D.Ippolito (radiologist), C.Maino (radiologist).
Oslo-Bergen: M.Vesterhus (hepatologist), G.Kemmerich (radiologist), I.Björk (radiologist).
Kings College: J.Nayagam (hepatologist), M.Seager (radiologist), M.Limbada (radiologist).
Stockholm: A.Bergquist (hepatologist), A.Grigoriadis (radiologist), S.Hamma (radiologist).
References: 1. A. Grigoriadis, K. I. Ringe, et al. 2022. Development of a prognostic MRCP-score (DiStrict) for individuals with large-duct primary sclerosing cholangitis, JHEP Reports,4,12. http://doi.org/10.1016/j.jhepr.2022.100595

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Imaging/ERCP

Deadline is May 15th, 2024. Write "Proposal for IPSCSG meeting" in the subject line. Send it to annika.roback@regionstockholm.se

Title of Abstract

14. Value of sarcopenia for prognostication in patients with PSC

Authors; Name, title (Mark presenting author with *) and Institution (s)

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Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background: Sarcopenia is defined as a general decrease in muscle strength, mass and function. It is often observed in patients with advanced chronic liver disease and has been associated with a higher risk of adverse outcomes. Magnetic resonance imaging (MRI) enables the quantification of muscle mass without the use of ionizing radiation, making it a suitable technique for opportunistic screening and follow-up measurements. The goal of this study is to assess the prognostic value of MRI-based quantification of muscle mass in patients with PSC with regards to the clinical course of the disease.

Methods: Retrospective study in patients with confirmed diagnosis of PSC and available MRI. Muscle mass is quantified on non-contrast axial T1-weighted sequences. Measurements are performed at the level of the cranial endplate of L3 in two ways: maximal transverse diameter of the right psoas (PMT) and total area of psoas muscle on both sides (PMA). Sarcopenia is defined according to previously published cut-off-values. Muscle mass and prevalence of sarcopenia is correlated with patient demographics (age, sex), disease characteristics (subtype, overlap, IBD, disease duration), liver functions tests, clinical scores (MELD, Mayo Risk) and solid endpoints (liver-related death, transplantation (LTx), cholangiocarcinoma (CCA).

Preliminary results: 231 PSC patients (152m/79f; mean age 41y) were included in a retrospective single-center study. At a mean follow-up of 7 years, 95 endpoints were observed in 80 patients (LTx n=57; CCA n=19; death n=19). 160 out of 231 included patients had concomitant IBD. Interrater agreement (two radiologists) for muscle mass measurements was almost perfect (PMT: ICC=0.91; PMA: ICC=0.96). Sarcopenia was prevalent in 27.7% and 51.5% of PSC patients, respectively (according to the definition of PMT and PMA). Sarcopenia was significantly more prevalent in female patients and in patients without concomittant IBD ($p<0.05$). A significant negative correlation of muscle mass was noticed with the MELD ($r=-0.247$, $p=0.001$) and Mayo Risk Score ($r=-0.133$, $p=0.04$). At follow-up, sarcopenia was associated with an inferior transplant-free survival ($p=0.025$).

Proposal: Multicenter, retrospective study on MRI-based quantification of muscle mass and prevalence of sarcopenia in patients with PSC for long-term prognostication of disease course. Decentralized image-analysis and muscle measurements are performed. Validation of previously published cut-off values for definition of sarcopenia and verification in PSC-specific cohort.

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Imaging/ERCP

Deadline is May 15th, 2024. Write "Proposal for IPSCSG meeting" in the subject line. Send it to annika.roback@regionstockholm.se

Title of Abstract

15. Usefulness of peroral cholangioscopy (POCS) in the diagnosis and follow-up of PSC

Authors; Name, title (Mark presenting author with *) and Institution (s)
Toshio Fujisawa MD*, PhD, Taito Fukuma MD, Muneo Ikemura MD, Haruka Hagiwara MD, Hiroyuki Isayama MD, PhD.
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Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background/rational:Although the characteristic ERCP findings of PSC are well known, the biliary mucosa findings that can be observed by per-oral cholangioscopy (POCS) have not been fully examined. In this study, we summarized POCS findings in PSC and examined whether POCS can contribute to the diagnosis and severity of PSC by comparing with ERC findings and observing changes over time.
Methods:We studied 18 cases who underwent POSC for PSC at Juntendo Hospital from 2018 to the present. First, the 11 POCS findings in PSC were classified into 3 categories: active, chronic, and tumorous, and how often each finding was seen in patients with PSC. We then compared POCS findings with those of the bile duct mucosa at locations consistent with the five representative ERC findings of PSC (Band-like stricture, Beaded appearance, etc.). In 8 cases that could be observed multiple times over time, changes in each of the findings of active, chronic, and tumorous were examined. Finally, we examined characteristic POCS findings in PSC compared with POCS in diseases other than PSC, such as cholelithiasis and cholangiocarcinoma.
Preliminary results: Four POCS findings of Mucosal erythema, Ulceration, Fibrinous white exudate, and Irregular surface were classified into Active findings and may reflect strong inflammation in the biliary epithelium. On the other hand, 3 findings of Scarring, Pseudodiverticula, and Bile duct stenosis were classified into the Chronic findings and may reflect fibrosis and stenosis resulting from repeated inflammation. The remaining 4 findings of Dilated vessels, Tortuous vessels, Friability, and Mass forming were classified into Tumorous findings as findings in which the combination of cancer could not be ruled out. Scarring was the most common POCS finding in PSC patients at 89%, and chronic findings were more common overall. In comparison with ERC findings, multiple POCS findings were mixed for one ERC finding, but since Band-like stricture and Beaded appearance showed Bile duct stenosis, Shaggy appearance showed Scarring, and Diverticulum-like outpouching showed Pseudodiverticula at 100%, these chronic POCS findings were considered to be mucosal changes underlying each ERC finding. Active and Tumorous findings ranged from improving to worsening over time, but chronic findings remained unchanged or worsened only, and no cases improved over time. Chronic findings were significantly more common in PSC than in other diseases ($p < 0.001$), and Pseudodiverticula in particular was a very characteristic finding in PSC alone.
What you ask for- your proposal:POCS offers not only information regarding the diagnosis of PSC and PSC-associated cholangiocarcinoma but also the current statuses of biliary inflammation and stenosis. POCS, especially focusing on chronic findings, may contribute to diagnosis and treatment decisions.

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Imaging/ERCP

Deadline is May 15th, 2024. Write "Proposal for IPSCSG meeting" in the subject line. Send it to annika.roback@regionstockholm.se

Title of Abstract

16. The early dynamic changes of radiological and biochemical scores help identify a more aggressive PSC phenotype

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E. Catanzaro*, M. Peviani, E. Bonaiuto, F. Pezzato, M. Gambato, R. Motta, N. Cazzagon.
University of Padova, Padova, Italy

Body text (background/rational, methods, preliminary results, what you ask for- your proposal)
Background. The natural course of Primary Sclerosing Cholangitis (PSC) is variable but generally progressive towards the development of cirrhosis and its complications. Predicting the prognosis in PSC is still a matter of debate. Several prognostic factors associated with transplant-free survival have been identified, including serum markers, composite scores, biliary and parenchymal changes and elastography. The aim of this study was to assess whether the evolution of biochemical and magnetic resonance imaging (MRI) scores is associated with an increased risk of developing clinical outcomes.
Materials and methods. We conducted a retrospective analysis of patients diagnosed with large ducts, non-cirrhotic PSC, who underwent regular clinical and radiological follow-up with at least two consecutive MRIs closest to the diagnosis, available for review by an expert radiologist. The ANALI scores with and without gadolinium (Gd) were assessed in the two MRIs, and any increase in the ANALI scores was considered as radiological worsening. Demographic data and liver function tests were collected at the same timepoints as the MRI scans, and two scores, the Amsterdam Oxford Model (AOM) and the Mayo Risk Score (MRS), were calculated and stratified into low, intermediate and high risk categories. The progression of AOM and MRS was defined by the upgrade from one category to a higher one. Clinical outcomes considered included the development of recurrent cholangitis, cirrhosis, cirrhosis decompensation, liver transplantation, death from liver disease, and the development of hepatobiliary malignancies.
Preliminary results. A total of 45 patients were included, with a median age at diagnosis of 30 years(21-38) and at inclusion of 36 years(28-50) years. Twenty-eight (62%) patients were male. The median interval time between the two MRIs was 24 months(16–38), and the median follow-up after the second MRI was 69 months (50-90). Thirteen (29%) patients experienced radiological worsening, while 8(18%) and 7(16%) patients showed progression of the AOM and the MRS, respectively. The increases in ANALI without Gd and the MRS were associated with the risk of development cirrhosis during follow-up ($p \equiv 0.003$ and $p \equiv 0.001$, respectively). Additionally, the increase in ANALI without Gd during follow up was significantly associated with the need for liver transplantation ($p \equiv 0.001$). A trend towards a significant association between the increase in MRS and liver transplantation was also observed ($p \equiv 0.085$). Finally, patients who developed recurrent cholangitis during follow-up exhibited a progressive increase in ANALI without Gd ($p \equiv 0.003$).
Conclusion: The early dynamic changes in radiological and biochemical scores help identify identifying a more aggressive PSC phenotype. These preliminary findings suggest the potential utility of dynamic assessment of radiologic and biochemical scores for prognostic purposes and risk stratification. Further validation in larger cohorts is warranted.

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Imaging/ERCP

Deadline is May 15th, 2024. Write "Proposal for IPSCSG meeting" in the subject line. Send it to annika.roback@regionstockholm.se

Title of Abstract

17. The protective role of gallbladder presence and enlargement in patients with Primary Sclerosing Cholangitis: preliminary analysis of a multicentric study

Authors; Name, title (Mark presenting author with *) and Institution (s)
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Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background: In a proof-of-concept study of patients with Primary Sclerosing Cholangitis (PSC), gallbladder (GB) enlargement was suggested to have a hepatoprotective role. Moreover, the presence of the GB was associated with less severe PSC as compared to cholecystectomized patients. Similarly, in a mouse model of PSC, cholecystectomy caused an increase in hepatic bile acids content and circulating secondary bile acids, exacerbating cholangitis, ductular reaction, inflammation and liver damage compared to sham-operated mice. Aim: To assess the impact of GB on PSC severity. We compared liver function tests, liver stiffness and event-free survival in patients with normal-sized GB vs. patients with enlarged GB and patients with intact GB vs. cholecystectomized. Methods: This is a multicentric retrospective study. Inclusion criteria comprised patients diagnosed with large duct PSC between 2000 and 2020, with at least one magnetic resonance imaging (MRI) scan available for review (the closest to diagnosis) and a minimum follow-up of 12 months. Exclusion criteria encompassed small-duct PSC, secondary sclerosing cholangitis or IgG4-associated cholangitis, as well as patients with a history of liver transplantation or cirrhosis decompensation prior to inclusion, and those presenting with gallbladder disease (e.g. cholecystitis, polyps/ cancer) at the time of inclusion. Gallbladder volume was quantified via MRI, with a cutoff of 50 mL employed to define GB enlargement. Results: This analysis was conducted on a cohort of 173 PSC patients from two European Reference Centers and comprises 102 males, with 120 having concomitant IBD and a median age at inclusion of 39 years. The majority (67%) were treated with ursodeoxycholic acid (UDCA) at the time on inclusion. Among the included patients, 71 had an enlarged GB, 74 had a normal-sized GB, and 28 had previously undergone cholecystectomy. Patients with enlarged GB, compared to those with normal GB volume, exhibited significantly lower alkaline phosphatase levels (ALP) (p= 0.027) and total bilirubin levels (p=0.037), as well as a longer duration of UDCA treatment (p=0.003). Additionally, they showed a trend towards longer mean adverse-event-free survival from inclusion according to univariate analysis (p=0.07). In the UDCA-treated group (n=93 patients), we observed that patients with enlarged GB, compared to those with normal GB, had lower frequency of cirrhosis at inclusion (p=0.016), lower levels of ALP (p=0.050) and total bilirubin levels (0.021) and a longer mean adverse-event-free survival according to univariate analysis (p=0.014). Furthermore, cholecystectomized patients, compared to those with intact GB, exhibited significantly lower levels of albumin at inclusion (p=0.03), but no difference in event-free survival. Conclusions: Taken together, these findings provide further evidence for a protective role of the GB in PSC. Validation is currently underway in a larger population.

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Imaging/ERCP

Deadline is May 15th, 2024. Write "Proposal for IPSCSG meeting" in the subject line. Send it to annika.roback@regionstockholm.se

Title of Abstract

18. Complications of ERCP and sphincterotomy in primary sclerosing cholangitis

Authors; Name, title (Mark presenting author with *) and Institution (s)

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Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease that leads to fibrosis and strictures of the bile ducts and is associated with an increased risk of cholangiocarcinoma (CCA). Endoscopic retrograde cholangioscopy (ERCP) is an established endoscopic procedure for the treatment of bile duct strictures with signs of obstructive cholestasis and suspicion of malignancy.

Aim

The aim of this study was to investigate the frequency for the occurrence of ERCP associated complications in the context of cannulation and primary sphincterotomy in patients with PSC.

Methods

A retrospective study was conducted to investigate the frequency for ERCP associated complications in patients with PSC who underwent sphincterotomy compared to matched control patients without PSC between January 2016 and December 2023 in a tertiary centre. Procedural and clinical data were collected. Peri- and post-interventional complications were defined as the occurrence of pancreatitis, cholangitis, perforation and bleeding within 14 days after ERCP.

A total of 59 patients with PSC underwent ERCPs with sphincterotomy. A control group of 118 patients without PSC receiving ERCPs and sphincterotomy were matched by age and sex (1:2).

There was no significant difference in the overall complication rate between the two groups [n=18 (30.5%) vs. n= 25 (21.2%); p=0.17; OR 1.7, CI 0.8 – 3.3).

The incidence of post-ERCP cholangitis was significantly higher in the PSC cohort compared to the control group (n=6 (10.2%) vs. n=2 (1.7%); p=0.01; [OR 6.6; CI 1.3-33.6]).

There was no significant difference between the PSC cohort and the matched control group in terms of post-ERCP-pancreatitis (PEP), which occurred in 11 cases (18.6%) in the PSC cohort compared to 17 cases (14.4 %) in the control group (p=0.47). Bleeding rate [n=1 (1.7%) vs. n= 6 (5.1%); p=0.42] and perforation rate [n=2 (3.4%) vs. n=2 (1.7%); p=0.60] did not differ significantly.

Conclusion:

In patients with PSC, ERCP with sphincterotomy is not associated with an increased overall complication rate. However, there is a higher risk of cholangitis in patients with PSC, despite the majority receiving antibiotics. Although not statistically significant, there was a trend towards a higher rate of PEP in patients with PSC. For ERCP with sphincterotomy, careful indication and technique as well as the implementation of prophylactic measures are of crucial importance in this vulnerable patient group.

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Imaging/ERCP

Deadline is May 15th, 2024. Write "Proposal for IPSCSG meeting" in the subject line. Send it to annika.roback@regionstockholm.se

Title of Abstract

19. Genome-scale autoantibody profiling in primary sclerosing cholangitis provides an ATLAS of autoimmune traits associated with clinical phenotypes and disease progression

Authors; Name, title (Mark presenting author with *) and Institution (s)
Martin Cornillet*, Aiva Lundberg Bave, Dan Sun, Christina Villard, Aristeidis Grigoriadis, Erik von Seth, Hannes Jansson, Per Stål, SweHep, Ernesto Sparrelid, Niklas Björkström, Jonas Halfvarsson, Annika Bergquist. Karolinska Institute, Sweden

Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Rational
Primary sclerosing cholangitis is a rare cholestasis liver disease with heterogeneous phenotypes and progressions. Autoimmune traits, such as autoantibodies are suspected to drive its heterogeneity; we hereby search for those.

Method
We performed a genome-scale autoantibody screen of IgG and IgA isotypes using 42 170 protein fragments. This was followed by quantification of 1 153 selected autoantibody, in 500 PSC and 220 controls serum samples in a longitudinal setting using the SUPRIM cohort.

Results
We identified autoantibodies associating with clinical phenotypes, biochemical and clinical severity, comorbidities, and disease progression. Our data showed that instead of a single autoantibody marker of the disease, small groups of patients were positive for various autoantibodies with highly variable diagnostic specificity. Global deconvolution of autoantigens targets showed overrepresentation of proteins normally expressed in immune privileged sites at steady state such as the brain, testis, and retina. Interrogating tissue-specific autoantigens co-expression linked to expression and splicing quantitative traits loci of PSC risk variants, thyroid was additionally identified as relevant tissue. Finally, we identified an increased diversity of autoantibodies associating with PSC duration and end-stage disease already detectable several years before liver transplantation.

Conclusions
Our results are provided as a resource for further studies. Overall, our data provided evidence supporting the cryptic antigen and the epitope drifting autoimmune theories, and a neuro-endocrine deregulation as mechanisms potentially involved in PSC pathogenesis.

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Pathogenesis

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Title of Abstract

20. The role of interleukin-8 in primary sclerosing cholangitis-associated immune cell dysregulation

Authors; Name, title (Mark presenting author with *) and Institution (s)

*Lander Heyerick (1,2), Kevin De Muynck (1,2), Zenzi De Vos (1,2), Sander Lefere (2,3), Jana Roels (4,5), Niels Vandamme (4,5), Malaika Van Der Linden (6), Anne Hoorens (6), Anja Geerts (2,3), Sarah Raevens (2,3), Xavier Verhelst (2,3), Hans Van Vlierberghe (2,3), Lindsey Devisscher (1,2).

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Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background and Aims: Primary sclerosing cholangitis (PSC) is a chronic, progressive, fibroinflammatory liver disease. Dysregulated systemic and hepatic immune cell responses are implicated in the pathogenesis of PSC and could serve as a diagnostic and therapeutic target. However, PSC-associated systemic immune cell profiles remain insufficiently characterised. Therefore, we unravelled peripheral immune cell subsets of PSC patients and healthy controls at the single cell level and further investigated its implications in PSC pathogenesis.

Method: Peripheral blood mononuclear cells (PBMCs) were isolated by density gradient centrifugation from fresh EDTA-anticoagulated peripheral blood from PSC patients and healthy controls (HCs). PBMC cell suspensions were: a) FACS-purified, single cell Gel Bead-in-Emulsions were generated and RNA-sequencing libraries were created and analysed, or b) evaluated for interleukin-8 (IL-8) expression in $CD14^+$ cells by flow cytometry. IL-8 concentrations were determined in the sera of PSC-patients, without prior liver transplantation, and of healthy controls. Adult male C57BL6/J mice were subjected to common bile duct ligation (CBDL) surgery and a) after two weeks, monocyte/macrophage populations were sorted by FACS and processed for bulk sequencing, or b) mice were treated 12 days with reparixin (a potent CXCR1- and weak CXCR2-antagonist), SB225002 (a selective CXCR2-antagonist), navarixin (a dual CXCR1/2 antagonist) or with vehicle.

Results: Based on single cell analyses of PBMCs, we identified a population of CD14-positive monocytes with enriched IL8-expression in PSC patients (n=7) compared to HCs (n=4), which was confirmed on flow cytometry analyses (mean expression 52.9% in PSC and 12.2% in HC, $p<0.05$). Serum protein analyses showed that PSC patients are also characterised by increased IL-8 levels in the systemic circulation (n=57 for PSC, n=15 for HCs, age- and sex-matched). In addition, PSC patients with advanced fibrosis (Metavir stage F3/F4) had significantly higher serum concentrations of IL-8 compared to patients without advanced fibrosis (F0/F2, $p<0.05$). AUROC analysis showed good performance of IL-8 to assess risk of liver-transplant free survival at 3 years of follow-up (AUROC 0.78). Bulk sequencing of isolated mouse liver monocyte-derived macrophages in CBDL-induced cholestasis showed significantly upregulated expression of the IL-8 mouse homologs Cxcl1 and Cxcl2 2 weeks after surgery compared to sham-operated mice. Moreover, reparixin-treated mice exhibited no significant upregulation of proinflammatory and fibrotic markers in comparison to sham-operated mice, while this was the case for vehicle-, SB225002- and navarixin-treated mice.

Conclusion: PSC patients are characterised by a population of CD14-positive monocytes enriched in IL8-expression and by elevated IL-8 concentrations in the systemic circulation. Serum IL-8 concentrations might serve as prognostic marker for liver-transplant free survival. Reparixin, a dual CXCR1/2-antagonist with increased selectivity for CXCR1, suppresses CBDL-induced liver injury and further research should focus on unravelling its potential as a therapeutic target.

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Pathogenesis

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Title of Abstract

21. Assessing the Gut Barrier Dysfunction in Pediatric Sclerosing Cholangitis through a Metagenomic and Metabolomic analysis of Mucosal Microbiome (MuMi Study).

Authors; Name, title (Mark presenting author with *) and Institution (s)
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Hepatology and Gastroenterology Unit, Bambino Gesu' Children Hospital, Rome, Italy

Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Sclerosing Cholangitis (SC), either in its primary (PSC) or autoimmune (ASC) form, present similar progression to adverse outcomes and/or end-stage liver disease, despite different medical therapies have been proposed over the years. The strong association between SC and Inflammatory Bowel Diseases (IBDs) represents a cornerstone of the disease, leading SC focus toward the study of Gut-Liver axis (GLA). Most of the recent studies have focused on the faecal microbiota role, however recent evidences have shown how the identification of a specific mucosa-adherent microbial signature may unveil more insights into the onset, recurrence, and outcome of SC. Therefore, the study of mucosal microbiota may represent a new avenue in understanding some of the unknown pathogenetic mechanisms and ideally validate markers of disease severity.

This study, that will be held at our tertiary level pediatric hospital (Bambino Gesu' Children Hospital in Rome), aims to identify a potential modifiable disease pathway by evaluating differences in metagenomic and metabolomic profiles investigating intestinal mucosa samples obtained during colonoscopy (terminal ileum [TI], ascending colon [AC], descending colon [DC], transverse colon [TC]) in a cohort of 20 pediatric patients with SC and compared with a cohort of 20 IBD-only patients (IBDo) and 20 healthy controls (HC).In order to stratify the study population, SC patients will be divided into two subgroups with PSC and ASC form. Subgroups will be further divided according to the presence of an associated IBD (PSC +/- IBD and ASC +/- IBD).

The primary endpoint is the evaluation of the mucosal microbiome by 16s ribosomal RNA sequencing to obtain data on beta and alpha diversity and taxonomic composition for comparison between the main groups and subgroups above. The same analysis will be performed, on faecal microbiome of the same study population, to investigate differences with the data obtained from mucosal samples.

Secondary endpoints include the study of mucosal permeability status in patients with SC and its subgroups, analyzing serum intestinal barrier biomarkers (lipopolysaccharide and zonulin), plasma metabolites (vitamin B6, biliary acids) and branched-chain amino acids (BCAAs). The latter have been associated with reduced liver transplant-free survival in SC due to their decreased metabolic pathway in the microbiome of PSC patients.Statistical analysis between groups will be performed using Student's test (t-test) and One-way ANOVA for parametric variables.

To the best of our knowledge, this is the first proposal, of a single-centre prospective study, investigating in depth the role of the gut mucosal microbiome and intestinal permeability in a cohort of paediatric patients with SC.

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Pathogenesis

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Title of Abstract

22. Intergenic risk variant rs56258221 skews the fate of naive CD4+ T cells via miR4464-BACH2 interplay in primary sclerosing cholangitis

Authors; Name, title (Mark presenting author with *) and Institution (s)
*Poch T Dr (1),Bahn J, Casar C, Krause J Dr, Evangelakos I Dr, Gilladi H Dr, Kunzmann LK Dr, Folseraas T Dr, Engesaeter LK Dr, Karlsen TH Prof, Schlein C Dr, Galun E Prof, Huber S Prof, Lohse AW Prof, Gagliani N Prof, Schwinge D Dr, Schramm C Prof. (1) UKE, Hamburg, Germany

Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background/rationale:
Primary sclerosing cholangitis (PSC) is an immune-mediated liver disease of unknown pathogenesis, with a high risk to develop cirrhosis and malignancies. Although functional dysregulation of T cells and association with genetic polymorphisms in T cell-related genes was previously reported for PSC, few studies so far investigated functional outcomes of carrying risk-genotypes.
Here, we aimed to determine functional outcomes of selected disease-associated T cell-related risk loci.
Methods:
We genotyped a representative PSC cohort (n=210) for several disease-associated risk loci and performed comprehensive immunophenotyping and in vitro differentiation assays. After correlating T cell phenotype and function to the underlying genotype, we performed single-cell RNA and ATAC sequencing on selected patients. Finally, we combined the PSC cohort from Hamburg with a representative cohort from Oslo, Norway, to assess clinical implications of carrying the genetic polymorphism rs56258221.
Results:
We identified rs56258221 (BACH2/MIR4464) to correlate with not only the peripheral blood T cell immunophenotype but also with functional capacities of naive CD4+ T cells in patients with PSC. The overall enhanced pro-inflammatory T cell profile in SNP-carriers was accompanied by skewed differentiation capacities of naive CD4 T cells towards pro-inflammatory subsets, i.e. Th1 and Th17, whereas differentiation towards iTreg was impaired. We were able to link these observations to decreased protein levels of BACH2 in carriers of rs56258221, which showed a concomitant increase of BACH2-targeting miR4464 expression. Assessing clinical data from two independent PSC cohorts revealed a trend towards accelerated disease progression in carriers of rs5625822, represented by a shorter transplant-free survival and elevated biomarkers routinely used to evaluate severity of disease.

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Pathogenesis

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Title of Abstract:

23. Distinct gene pathways and cell types define peribiliary disease states in PSC

Authors; Name, title (Mark presenting author with *) and Institution (s):

*Brian K. Chung[1, 2, 3], Markus S. Jördens[1, 2, 3, 4], Jonas Øgaard[1, 2], Tom Luedde[4], Tom H. Karlsen[1, 2, 3, 5], Espen Melum[1, 2, 3, 5, 6]

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Body text (background/rational, methods, preliminary results, what you ask for- your proposal):

Background and Aims: Primary sclerosing cholangitis (PSC) features progressive biliary infiltration, fibrosis and cholangiocyte destruction. To better understand the dynamics of PSC, we combined spatial with single-nuclear transcriptomics (snRNA-seq) to characterize the transcriptome and cellular composition of peribiliary regions in PSC explants from early to advanced disease.

Methods: Fresh-frozen liver explants from 21 PSC patients (transplant indication: 4 recurrent cholangitis, 7 dysplasia,10 cirrhotic) and 7 cirrhotic controls (4 alcoholic-related, 3 metabolic-dysfunction-associated steatohepatitis) were analyzed by spatial transcriptomics (Visium,10X Genomics). A subset of the same explants (12 PSC, 4 controls) were assessed by snRNA-seq (Chromium 3', 10X Genomics) to create a patient-matched single-cell reference. Spatial and snRNA-seq transcripts were annotated by SpaceRanger/CellRanger (10X Genomics) and clustered using Seurat v5.0.0 (Satija Lab, Broad Institute/MIT). Differentially expressed genes (DEG) for spatial and snRNA-seq clusters were calculated using the exact negative binomial test (Benjamini-Hochberg corrected) and DEG between PSC and controls were identified by Pseudobulk. All reported DEG reached statistical significance (P-adj<0.001) and stated fold-changes represent averaged values. CIBERSORTx deconvolution (Alizadeh/Newman labs, Stanford University) was used to estimate enriched cell types at peribiliary regions using spatial transcriptomes and the patient-matched snRNA-seq reference.

Results: To determine if the biliary microenvironment in PSC differs from controls and across stages of disease, we first integrated the spatial transcriptomes of all PSC and control livers and performed unsupervised clustering to identify common regions of early, intermediate and late disease by gene content. Areas of early disease defined by hepatocytes (*ALB*, *APOA1/2*, *APOC1/3*), intermediate characterized by fibrosis (*COL1A1/2*, *COL3A1*, *COL6A2*) and late-stage by dense B cell infiltration within fibrotic septa (*IGHA1*, *IGHG1*, *IGHM*) clearly corresponded to histological features observed by hematoxylin and eosin staining of the same tissue sections. Local profiling of *KRT19+CFTR+* peribiliary regions by spatial transcriptomics revealed robust upregulation of metallothionein-related *MT1E*, *MT1G* and *MT1H* (14.9-fold) and inflammatory *SAA1* and *SAA2* (8.4-fold) by peribiliary hepatocytes at early and intermediate stages of PSC compared to controls. *VCAN+* tissue monocytes and *MARCO+* Kupffer cells were also over-represented around early PSC bile ducts (1-2% of total cells vs undetectable in controls) whereas *FCRL1+BANK1+* B cells were expanded 1.5-fold at intermediate and late-stage PSC bile ducts versus controls.

Conclusions: Peribiliary regions at different stages of PSC express shared and distinct gene profiles compared to disease controls that correspond to enrichment of specific cell types. Overlapping signatures may signify consistent drivers of PSC whereas genes unique to each disease state could represent temporal disease mechanisms.

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Select which of the following topics your abstract belongs to: Pathogenesis

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Title of Abstract

24. Enterococcus faecalis virulence determines intestinal barrier translocation in murine sclerosing cholangitis

Authors; Name, title (Mark presenting author with *) and Institution (s)
Victor Haas *(1), Philipp Dirksen (2), Cornelia Gottwick (1), Vera Grafen (1), Nicola Iuso (1), Franziska Mangler (1), Lukas Middendorf (3), Dorothee Schwinge (1), Christoph Schramm (1,4)
(1) University Medical Center Hamburg Eppendorf, Department of Internal Medicine I.

Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

BACKGROUND AND AIMS
Primary Sclerosing Cholangitis (PSC) is a disease characterized by bile duct inflammation and scarring. Bile ducts can become colonized by bacteria, and we showed that positive bile cultures for Enterococcus sp. associated with transplantation-free survival in PSC. Given the unexplored role of biliary colonization and its potential influence on biliary immunoregulation, we aimed to investigate E. faecalis colonization dynamics in PSC.

METHODS
Bile and stool from people with PSC and controls were collected. E. faecalis isolates were retrieved and sequenced, and virulence genes annotated (VFDB). For functional assays, we challenged H69 human cholangiocytes with stool-derived E. faecalis lysates, and measured Interleukin-6 concentration by ELISA. We gavaged selected isolates to antibiotic pre-treated mice affected by sclerosing cholangitis (Mdr2-/-) and assessed bacterial translocation to the mesenteric lymph nodes and liver. Liver injury was evaluated by histology, gene expression and serum enzymes measurement.

RESULTS
Genomic analysis highlighted diverse patterns of virulence in bile and stool E. faecalis. The presence of the genes esp and gelE positively correlated with IL-6 production in vitro. Virulent E. faecalis translocated to the mesenteric lymph nodes of Mdr2-/- mice more frequently than non-virulent E. faecalis and induced significantly higher expression of pro-apoptotic Casp8 in the liver. Overall, E. faecalis virulence genes determine its inflammatory potential in vitro and its ability to cross the intestinal barrier in Mdr2-/- mice. These results support the notion that E. faecalis virulence could be relevant in PSC disease course. Further work is needed to assess whether these findings translate into the context of human bile ducts.

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Pathogenesis

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Title of Abstract

25. Pathological Klebsiella pneumoniae determines the clinical course of primary sclerosing cholangitis and potentially serves as therapeutic targets.

Authors; Name, title (Mark presenting author with *) and Institution (s)
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Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background and Aims: Primary sclerosing cholangitis (PSC) is a cholestatic liver disease characterized by progressive biliary inflammation and fibrosis with a frequent complication of inflammatory bowel disease (IBD). We recently reported that specific gut microbiota, Klebsiella pneumoniae (Kp), Proteus mirabilis (Pm), and Enterococcus gallinarum (Eg), were frequently present in faecal samples from patients with PSC+IBD and the combination of these three gut bacteria contributed to the pathogenesis of the hepatobiliary phenotype. As a mechanism of pathogenesis, these bacteria translocated to mesenteric lymph nodes (MLN) and contributed to subsequent T helper 17 (TH17) cell induction in the liver. However, it remains unclear whether the abundance or combination of these microbiota is associated with the clinical outcome of PSC, and whether certain bacteria might serve as therapeutic targets. As a therapeutic tool for targeting specific gut microbiota, we developed a lytic bacteriophage cocktail specifically targeting PSC-derived Kp strains, which demonstrated a sustained suppressive effect in vitro.
Method: We collected faecal samples from 45 PSC patients, either complicated with IBD (n = 34) or without IBD (n = 11) and investigated whether carriage of each bacterium or its combination could affect the clinical course. Germ-free (GF) mice and specific pathogen free (SPF) mice were inoculated with PSC-derived Kp and administered with the phage cocktail, and Kp levels in faecal samples were measured. 16s rRNA metagenome analysis was used to examine the effect of phage cocktail on the overall gut microbiota composition of faecal samples. Furthermore, to examine the effect of phage cocktail on experimental hepatobiliary injuries, Kp-colonized mice were given phage cocktail or vehicle orally or intravenously three times a week during 3, 5-diethoxycarbonyl- 1, 4-dihydrocollidine (DDC) feeding for three weeks.
Results: We detected abundant Kp and Eg in faecal samples from 45 patients with PSC regardless of intestinal complications (Kp: PSC, 82% vs. PSC+IBD, 82%; Pm: PSC, 21% vs. PSC+IBD, 9%; and Eg: PSC, 73% vs. PSC+IBD, 76%). Carriers of both Kp and Eg (n = 28) exhibited higher serum ALP levels and poorer transplant-free survival compared to non-carriers (n = 17). Colonization of PSC-derived Kp in hepatobiliary injury-prone mice enhanced liver Th17 cell responses and exacerbated hepatobiliary injury through bacterial translocation to MLN. Oral administration of the phage cocktail reduced intestinal Kp levels in Kp-colonized mice by 2 log without inducing off-target dysbiosis. Furthermore, oral and intravenous administration of phage cocktail reduced Kp levels in hepatobiliary injury-prone SPF mice, and attenuated liver Th17 numbers, hepatobiliary inflammation, and fibrosis progression. Of note, the amount of Kp in the MLN significantly correlated with the degree of fibrosis in the phage-treated mice, suggesting that a direct targeting of the translocated Kp by the intravenous administration may be a more appropriate therapeutic approach.
Conclusion and proposal: Our results identified a clear association between specific gut microbiota Kp and the clinical course of PSC, and revealed that targeting a single Kp pathogen is promising for the treatment of PSC.

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Pathogenesis

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Title of Abstract

26. Studying mechanisms of primary sclerosing cholangitis *in vitro* using a bile duct on a chip

Authors; Name, title (Mark presenting author with *) and Institution (s)

Henry W. Hoyle[1,2,3,4] *, Anna K. Frank[1,2,3,4,5], Mathias Busek[4,6], Aleksandra Aizenshtadt[4], Fotios Sampaziotis[7,8,9,10], Tom H. Karlsen[1,2,3,11], Stefan Krauss[4,6] and Espen Melum[1,2,3,4,11§]

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Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background:

Investigations into disease processes in primary sclerosing cholangitis (PSC) are hindered by a lack of effective laboratory models, with mouse models being still the gold standard. Cholangiocyte organoids have become a powerful *in vitro* tool although with drawbacks such as lack of a tubular structure and limited access to their apical interior, limiting the range of studies that they can be used for. To address these shortcomings, we have created an *in vitro* bile duct on a chip model incorporating patient derived primary human cholangiocytes. This provides a platform for studies ranging from basic cholangiocyte biology to modelling PSC.

Methods:

A collagen gel containing a hollow channel was formed within a 3D printed bile duct chip. Primary human cholangiocytes derived from brushings taken during endoscopic retrograde cholangiopancreatography (ERCP) were seeded to the channel and cultured in the chip for approximately 7 days. The properties of the bile duct on a chip system were investigated using confocal microscopy and biochemical assays. Functional properties of the cholangiocytes were also tested using fluorescent transport assays, with drug treatments to investigate the impacts of transport inhibition.

Results:

A robust and well differentiated epithelial monolayer with clear similarity to the *in vivo* bile duct formed around the channel lumen after approximately 7 days of culture with human cholangiocytes. To demonstrate the effective epithelial barrier, a fluorescent-labeled dextran permeability assay was used. Dextran molecules of different sizes (3, 10, 40, 70kDa) were all effectively contained by the epithelium, while addition of lipopolysaccharide (LPS) impaired this barrier function. Staining for proteins such as actin, zonula occludens-1 (ZO-1) and multidrug resistance-associated protein 3 (MRP3) demonstrated a strong apical-basal cellular polarization. Active transport of molecules across the epithelium was proven using the rhodamine 123 assay and this could be inhibited through the addition of verapamil.

Conclusion and future directions:

This model represents an *in vitro* bile duct demonstrating relevant functional features of a bile duct *in vivo*. The use of patient derived cholangiocytes allows the model to be adapted for PSC or healthy patients to explore variability between these groups. A broad range of future PSC studies can be carried out using this model, with potential incorporation of factors such as circulating immune cells, cytokines and gut microbiota.

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Pathogenesis

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Title of Abstract

27. Single-cell sequencing of PSC patient liver tissue identifies an altered immune landscape and characterizes epithelial and stromal responses

Authors; Name, title (Mark presenting author with *) and Institution (s)

Jake Herb*[1], Ksenija Sabic[1], Jiayu Zhang[1], Christopher Tastad[1], Judy Cho[1]
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Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background
PSC is an immune-mediated disease of the biliary epithelium characterized by periductal fibrosis of the medium and large bile ducts. Pharmacological treatments for PSC remain limited in part due to an incomplete understanding of the disease pathogenesis, especially in regards do the immunologic and pro-fibrotic factors that drive periductal fibrosis in these patients. This study aims to define the cellular and molecular drivers of periductal fibrosis in PSC using single-cell analysis of patient liver tissue.

Methods
Formalin-fixed paraffin-embedded (FFPE) liver tissue was collected from eighteen patients undergoing liver transplant or resection at Mount Sinai Hospital between 2018-2024. This cohort included ten PSC patients (n = 10) and eight patients with metastatic colorectal cancer (n = 8) who served as controls. Control tissue was collected from the tumor-free margin. scRNA-seq was performed on this FFPE tissue using the 10X Genomics "FLEX" Fixed-RNA Profiling (FRP) workflow. Cells were projected onto reference datasets within CellTypist to facilitate detailed immune-cell annotation. Ligand-receptor interactions were assessed with CellChat.

Results
In total, we identified 80,044 high-quality cells and identified 27 distinct cell types. We observed expanded populations of Th1, Th17 and Treg cells [$p \leq .011$] in the PSC samples but not CD8 T-cells. Cholangiocytes from PSC samples displayed an activated phenotype characterized by increased expression of cytokines, including IL8, IL32, and TGFβ [$p \leq 2.3x10^{-14}$]. We found differences in gene expression between PSC samples and controls across stromal, endothelial, epithelial, and immune cell subsets; of note, portal-endothelial cells, fibroblasts, and myofibroblasts displayed induction of IL6 [$p \leq .008$]. CellChat analysis identified GDF15-TGFBR2 and FGF23-FGFR1 as ligand-receptor interactions uniquely active in the PSC samples.

Conclusions
We describe an altered cellular landscape in the PSC liver, characterized by an expanded CD4 T-cell compartment and activation of both epithelial and stromal cells. Furthermore, we show that cholangiocytes in PSC induce expression of TGFβ, suggesting that the biliary epithelium is a key source of pro-fibrotic cytokines that drive periductal fibrosis. Cell-cell interactions will be validated in intact tissues using selected RNA and protein analytes with a focus on periportal regions.

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Select which of the following topics your abstract belongs to: **Pathogenesis**

Deadline is May 15th, 2024. Write "Proposal for IPSCSG meeting" in the subject line. Send it to annika.roback@regionstockholm.se

Title of Abstract

28. Tissue resident natural killer (NK) cells in the human biliary tract system

Authors; Name, title (Mark presenting author with *) and Institution (s)
Daniel Geanon*, Martin Cornillet, Christopher Maucourant, Anna Frank, Xiaojun Jiang, Ernesto Sparrelid, Annika Bergquist, Erik von Seth, Espen Mellum, Niklas Björkström
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Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Immune cells have been implicated in propagating biliary tract disorders such as primary sclerosing cholangitis (PSC), yet our understanding of the biliary immune microenvironment remains incomplete. Innate lymphoid cells (ILCs) have been described in other organ systems and have been shown to play essential roles in orchestrating immune responses and maintaining tissue homeostasis. However, whether ILCs populate healthy and diseased bile ducts in humans has yet to be elucidated. Therefore, in this study we set out to characterize biliary natural killer (NK) cells in PSC patients utlizing technologies such as flow cytometry, single-cell RNA sequencing (scRNA-seq), and MACSima imaging. We identify biliary resident NK cells that are phenotypically and functionally distinct from liver resident NK (lrNK) cells, most notably in their expression of integrins CD49a and CD103. In vitro experiments leveraging cholangiocyte organoid models demonstrate that cholangiocyte derived TGF-b drives this tissue residency process. We hypothesize that stressed and/or damaged cholangiocytes produce increased levels of TGF-b in vitro and in vivo, and this in turn dampens biliary resident NK cell effector function in disease. Future perspectives include expanding upon our co-culture organoid system by addition of disease relevant cytokines, as well as scRNA-seq of biliary immune cells from a liver transplantation cohort to explore mechanisms of biliary NK cell tissue residency in vivo. Summarizing, this study adds to our knowlege of the biliary immune microenvironment in humans, and our goal is to learn how other researchers are employing state-of-the-art immunlogical techniques to study the local immune system in PSC patients.

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Pathogenesis

Select which of the following topics your abstract belongs to:

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Title of Abstract, 29

Single-nuclei sequencing of human liver samples reveals heterogeneity and compositional changes of biliary epithelial cell subpopulations during the progression of primary sclerosing cholangitis

Authors; Name, title (Mark presenting author with *) and Institution (s)
Laura Liebig*; Eric Lindberg, Dr.; Elenora Adami, Dr.; Natalia Lopez Anguita, Dr.; Giannino Patone, Dr.; Alena Laschtowitz, Dr.; Silja Steinmann, Dr.; Marcial Sebode, Dr.; Nicola Gagliani, Prof. Dr.; Dorothee Schwinge, Dr.; Norbert Hübner, Prof. Dr.#; Christoph Schramm, Prof. Dr.#
#Authors share senior authorship

Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background/rational

In primary sclerosing cholangitis (PSC) biliary epithelial cells (BECs) are central targets of inflammatory responses. However, little is known about their composition, function, and role in the disease process. Within this project we aim to decipher the characteristics of BECs at different disease stages.

Methods

56 liver samples from people with PSC at early and late stages, metabolic liver diseases, autoimmune hepatitis and people with healthy liver tissue were processed by single nuclei sequencing. To resolve the location of cell states, spatial transcriptomic techniques were performed.

Preliminary results

We were able to identify seven BEC states. Compared to healthy liver tissue, a BECs population, characterized with a progenitor-like phenotype, was significantly decreased already at early PSC stages with a further gradual reduction from early to later PSC stages. In PSC, this population showed an upregulation of genes important for recruiting and engaging with T cells (CCL20, HLA- DQB1, ICAM1). Similarly, a population of mature bile duct cells, was reduced in PSC and showed an enrichment of the TNF-a signaling pathway. In contrast, BECs characterized by an upregulation of genes involved in inflammatory processes, fibrosis, and recruitment of myeloid cells (ICAM1, CXCL2, S100A6, NFKB1, LDLR, FGF13, FN1, LAMC2, IL6R, MET, NFKB1), showed a gradual and significant increase from early to later PSC stages. Additionally we identified a BECs population with hepatocyte-like phenotype (ASGR1, KRT23), which was significantly enriched in cirrhotic PSC livers compared to healthy controls. Spatial transcriptomic analysis confirmed the presence of this cell state around the periductal fibrotic scar region. By comparing the compositional changes in the BECs compartment between PSC and other liver diseases such as autoimmune hepatitis or metabolic dysfunction-associated steatotic liver disease we could confirm that these changes were specific for PSC.

In this study we define specific BEC states involved in the progression of PSC. In early PSC stages, our data suggest the engagement of BECs with myeloid cells, whereas in later stages of disease, a population of BECs that potentially derive from transitioning hepatocytes may contribute to disease pathogenesis. Our findings present comprehensive insights into the heterogeneity of BECs and their role in different human liver diseases and show detailed composition and gene expression changes during the progression of PSC.

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Pathogenesis

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Title of Abstract

30. THE CONCENTRATIONS OF TNFRSF14 AND LIGHT IN THE SERA AND BILE OF THE PATIENTS WITH PRIMARY SCLRELOSING CHOLANGITIS

Authors; Name, title (Mark presenting author with *) and Institution (s)
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Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

【Background】
Primary sclerosing cholangitis (PSC) is an idiopathic cholestatic disease. Recent genome-wide studies (GWAS) have identified about 30 disease susceptible genes to PSC. We investigated the expression profiles of these genes in the liver biopsy samples of the patients with PSC, and revealed that the expression of TNFRSF14, which is a one of the risk genes for PSC, was upregulated in the biliary epithelial cell (BEC) of PSC compared to that in normal liver tissue and primary biliary cholangitis (PBC) liver tissue. TNFRSF14 is a member of the tumor necrosis factor receptor superfamily associated with inflammation and fibrosis. We also clarified that the expression of LIGHT, an active ligand for TNFRSF14, was elevated in the BEC of PSC 1). These molecules are expressed on lymphocytes and various tissues, and have two types of form: membrane binding and soluble forms. In other inflammatory diseases, many reports have mentioned to the associations between these molecules in the sera and the disease progression.
【Aims】 In this study, we aimed to evaluate the concentrations of these molecules in the bile of PSC, comparing with those of the other cholestatic disease.
【Methods】 The samples were collected from the 15 patients with PSC, 12 patients with malignant biliary obstruction (MBO), 19 patients with biliary lithiasis (BL) during endoscopic retrograde cholangiopancreatography. The concentrations of soluble TNFRSF14 and LIGHT in the bile were measured by enzyme-linked immunosorbent assay. The median values of the bile concentrations (b) of each group were evaluated by Mann-Whittney U test.
【Results】 bTNFRSF14 of the PSC group was 2,005 pg/mL, showing no significant difference compared to those of the MBO (1,794 pg/mL, $P = 0.516$) and the BL group (1,987 pg/mL, $P = 0.504$). On the other hands, bLIGHT of the PSC group was 523 pg/mL, remarkably higher than those of the MBO (82 pg/mL, $P < 0.001$) and the BL group (268 pg/mL, $P = 0.024$).
【Conclusions】 The elevated bile concentration of LIGHT can be involved in in the unique biology of PSC. Further research is needed to elucidate the interaction between these two molecules on biliary epithelial cells.

1) Digestive Liver Disease 2024 Feb;56(2):305-311.

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Pathogenesis

Deadline is May 15th, 2024. Write "Proposal for IPSCSG meeting" in the subject line. Send it to annika.roback@regionstockholm.se

Title of Abstract

31. PSC-IBD with IBD as a Comparator: Epidemiological Patterns in Incidence, Prevalence, and Outcomes at the Population Level

Authors; Name, title (Mark presenting author with *) and Institution (s)

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1Toronto Centre for Liver Disease, University Health Network, University of Toronto, Toronto, Canada ;2 Institute for Clinical Evaluative Sciences (ICES) Queen's, Kingston, Canada; 3Erasmus Medical Center, Rotterdam, Netherlands; 4The Hospital for Sick Children, University of Toronto, Toronto, Canada; 5ICES, Toronto, Canada; 6Kingston Health Sciences Center, Queen's University, Kingston, Ontario

Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background/Rational: Epidemiological study of PSC has been hampered due to its rarity as well as lack of a disease-specific code. As Ontario is Canada's most populous and diverse province (~15 million) with universal health coverage and routinely collected healthcare administrative data, it is well-suited for epidemiological studies of both PSC and IBD. We sought to evaluate epidemiological patterns in incidence, prevalence, PSC-IBD related cancers, transplant, and death.

Methods: Using linked health administrative data held at ICES, we derived and validated PSC-IBD incidence and prevalence cohorts from 2002-2018, along with use of previously derived and validated IBD cohorts. Effects and trends from sex, age, and socioeconomic status (SES) were evaluated with incidence rate ratios and joinpoint modelling respectively. Outcomes with regards to transplant, death, cause of death, PSC-IBD related malignancies, and PSC-IBD related surgeries were evaluated. A subcohort with PSC-IBD and IBD alone diagnosed from 2002-2018 was examined to align disease observations periods for comparison.

Results: Incidence of PSC-IBD and IBD was 0.46 and 24.6/100,000 person-years (PY) respectively. Prevalence of PSC-IBD and IBD was 5.53 and 588/100,000 PY respectively. Incidence/prevalence of PSC-IBD rose over time, unlike IBD. Higher SES associated with highest PSC-IBD incidence rates and fastest incidence rise. IBD then PSC had higher risk of transplant/death compared to PSC then IBD (HR 1.34, 95%CI 1.02-1.75), driven by increased risk of death (HR 2.73, 95%CI 1.68-4.45). PSC-IBD had a 4.5-fold greater risk of transplant/death compared to IBD alone. Of 1046 incident PSC-IBD cases with PSC diagnosed (median age 45 y.o.), there were 325 deaths (31%) at median age 65 y.o. Of the 254 (78%) who had a reported underlying cause of death, 37% were liver-related (with 26% attributable to hepatopancreatobiliary malignancy), while 14% were luminal GI related. Of 55,067 incident IBD cases with IBD diagnosed between 2002-2018 (median age 38 y.o.), there were 4757 deaths (8.6%) at median age 74 y.o. Of the 3048 (64%) who had cause of death reported, cardiovascular (19%) and pulmonary (19%) diseases were the most common causes. There were more frequent hepatobiliary (HB) and colorectal cancer cases in PSC-IBD than IBD alone, as well as more ileostomies, pouch creation, and cholecystectomies ($p<0.001$). There was a 42-fold higher risk of death in those with HB cancer compared to outcome-free PSC-IBD. Development of HB cancer was 3.75-fold higher with a history of colon cancer compared to outcome-free PSC-IBD.

Conclusions: Population level data supports distinct epidemiological patterns amongst PSC-IBD compared to IBD, with worse outcomes seen in PSC-IBD directly related to their diseases. Further studies utilizing healthcare administrative data are vital to evaluate for similar trends on a population level.

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PSC- IBD

Deadline is May 15th, 2024. Write "Proposal for IPSCSG meeting" in the subject line. Send it to annika.roback@regionstockholm.se

Title of Abstract

32. Dietary Practices and Beliefs in Individuals with Primary Sclerosing Cholangitis

Authors; Name, title (Mark presenting author with *) and Institution (s)

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ERN RARE-LIVER PSC Working Group

Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background: Primary sclerosing cholangitis (PSC) is a progressive hepatic disease closely associated with inflammatory bowel disease (IBD). Typically, the disease progression is gradual, and the mean duration until onset of liver failure or the necessity for liver transplantation is approximately 20 years. However, the disease can range from a more actively advancing form with severe symptoms to a slowly progressive and asymptomatic disease. It is unknown if dietary patterns affect the progression of the disease, and descriptions of dietary intake in patients with PSC are scarce. When studying dietary practices and beliefs amongst IBD patients, Limdi et al. found that 60% of IBD patients believed they had worsening symptoms with certain foods. In addition, nearly half of the IBD patients had never received any formal dietary advice. Walmsley et al. conducted a questionnaire to assess patient-reported quality of care in PSC and found that half of the individuals with PSC reported the need for more information on food, diet and supplements.

Aim: Our aim is to investigate to what extent PSC patients adapt their diets because of their PSC, and if applicable, to what extent they adapt their diets because of their underlying IBD. We will also investigate what their primary sources of information about diet are.

Study design: Cross-sectional observational study

Data collection: A web-based questionnaire have been developed by modifying the questionnaire "Dietary Practices and Beliefs in Patients with Inflammatory Bowel disease". The questions will be translated to different langugages by members of the PSC working group. The questionnaire will be distributed by healtcare centres and patient organisations via the ERN RARE liver e-newsletter. Individual patient organisations will be invited to share the questionnaire withing their own patient communities via newsletters, social media channels and their own websites.

Research questions:

- Do individuals with PSC restrict their dietary intake because of their disease?
- Do individuals with PSC experience symptoms that affect their ability to eat as normal?
- Is there a difference in dietary beliefs between individuals with PSC-IBD and non-IBD?
- Are there geographical differences in dietary beliefs and practices in individuals with PSC in Europe?

Preliminary time plan:
The study idea was presented for the ERN RARE-LIVER PSC Working Group in March 2024 and many centres were interested to participate. In April and May 2024, we developed the questionnaire, which is now being distributed to patient representatives for testing. Following this, we will translate the questionnaire into various languages.

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PSC- IBD

Deadline is May 15th, 2024. Write "Proposal for IPSCSG meeting" in the subject line. Send it to annika.roback@regionstockholm.se

Title of Abstract

33. The bidirectional regulatory network of immune cells and cholangiocytes

Authors; Name, title (Mark presenting author with *) and Institution (s)
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Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

BACKGROUND AND AIM

Primary sclerosing cholangitis (PSC) is a rare cholestatic liver disease caused by a dysregulation of immune response against cholangiocytes. Importantly, cholangiocytes are not only targets but can modulate the immune response respectively. We hypothesize that the interaction between immune cells and cholangiocytes determines biliary inflammation and thus the pathogenesis of cholangiopathies. Our objective is to delineate the adaptive capacity of cholangiocytes in influencing immune cell proliferation, activation, and plasticity.

METHODS

Cholangiocytes organoids and T cells are co-cultured together. Organoids are generated from liver explant tissue derived from people with autoimmune cholangiopathies and non-immune mediated liver diseases. T cells are derived from peripheral blood mononuclear cells and investigated in HLA matched/mismatched and sex matched manner. Both cholangiocytes and T cells are analyzed comprehensively using spectral flow cytometry, microscopy as well as gene expression analysis. Inflammatory mediators in the supernatant are determined by ELISA and/or LegendPlex assay.

RESULTS

To enable direct cell-to-cell interaction, we have established and optimized in vitro co-cultures with 3-D cholangiocytes organoids and T cells based on “floating cholangiocytes organoids”, improving cell-to-cell contact. Cholangiocyte organoids are carefully suspended and cultured in medium containing up to 5% gel-based extracellular matrix (ECM). Of note, the polarization of floating organoids is directed with the basal membrane facing outwards (basal-out). For effective co-culture experiments, it is crucial to determine the appropriate medium that can support the growth and proliferation of both cell types while maintaining their physiological function. We tested and identified an optimal cell culture medium that allows immune cell proliferation, activation, and survival without compromising cholangiocyte stability. By culturing organoids with pre-activated CD4 cells in the optimized medium, we were able to demonstrate an inhibitory action of cholangiocytes on CD4 cells, resulting in the subsequent down-regulation of markers such as CD25 and HLA-DR. Notably, cholangiocytes assume an activated phenotype that modulates the immune response through the up-regulation of PD-L1, a key regulator involved in the suppression of T cell activation, and other molecules involved in antigen presentation. To corroborate the suppression of CD4 cells post co-culture, we observed diminished levels of pro-inflammatory factors such as INFg, TNFa, IL-8, and CCL20 in the supernatant.

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PSC- IBD

Deadline is May 15th, 2024. Write "Proposal for IPSCSG meeting" in the subject line. Send it to annika.roback@regionstockholm.se

Title of Abstract

34. Safety and Efficacy of Upadacitinib in patients with PSC-IBD

Authors; Name, title (Mark presenting author with *) and Institution (s)
Ida Schregel*, Emma Culver, Palak Trivedi, Sarah Al-Shakhshir, Jeremy Nayagam, Deepak Joshi, Alexandra Kent, Haim Leibovitzh, Oren Shibolet, Levy Cynthia, Adrielly Martins, Laura Cristoferi, Chiara Vigano, Pietro Invernizzi, Xavier Velhust, Gareth Parkes, Christoph Schramm

Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background and Aims:

PSC is closely associated with the occurrence of IBD. In previous studies, it was shown that tofacitinib, a Janus Kinase (JAK) 1/3 inhibitor approved for the treatment of ulcerative colitis, led to an improvement in colitis activity in the majority of PSC patients with associated colitis. There were no safety concerns in relation to PSC. In addition, there was a decrease in alkaline phosphatase in the subgroup that responded to tofacitinib with regard to their bowel disease (Schregel et al., 2023). Upadacitinib, a novel and potent orally administered select JAK-1 inhibitor, has been approved for the treatment of IBD in 2022/23 (Sandborn et al., 2020; Danese et al. 2022). Our aim is to assess safety and efficacy of this new drug on liver and bowel disease.

Methods:

Multicenter clinical data collection is conducted retrospectively at baseline, after 3, 6, 12 months and annually thereafter.

Preliminary results:

34 (68% male) patients with PSC (71% large duct, 9% small duct and 18% with variant syndrome) were included with a median age at diagnosis of 21 (IQR 17-31) years. Of those patients, 85% presented with ulcerative colitis and 15% with Crohn's disease. Most patients (83%) received at least two biologicals prior to treatment with Upadacitinib, of whom 18% received another JAKi. Of those patients with at least a 3-months follow-up (n=30), 14% patients discontinued Upadacinitb (two due to adverse events, two due to non-response). Adverse events occurred in 5 cases (hepatitis, perianal abscess, low WBC count, anal fissur). Of those with both baseline and follow-up colonoscopy available (n=10), mucosal appearance as assessed by Mayo endoscopic subscore significantly improved (median 1.9 vs 1.2, Z -2.33, p = .020). In the overall cohort, ALP levels non-significantly (p = .424 n = 24) dropped from a median of 268 to 247 U/l at 3-months follow-up while transient elastography showed a slight increase (p = .217, n =11) from a median of 5.9 to 6.9 kPa. However, overall AST levels did not significantly increase between baseline and 3-months follow-up (67 vs 66 U/l, p = .933, n = 23).

Proposal:

Our data show a good response of PSC-associated IBD in this pretreated cohort. However, follow-up data and more insights into subgroups are lacking due to the limited number of patients. Therefore, we would like to present our preliminary data to invite IPSCSG members to contribute to our study.

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PSC- IBD

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Title of Abstract

35. Alkaline phosphatase and clinical scores predict outcome in recurrent primary sclerosing cholangitis after liver transplantation

Authors; Name, title (Mark presenting author with *) and Institution (s)
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Body text (background/rational, methods, preliminary results, what you ask for- your proposal)
Background/rational: Recurrent primary sclerosing cholangitis (rPSC) following liver transplantation for PSC is a clinical problem associated with increased graft loss and mortality. There is no therapy available to prevent rPSC or reduce disease progression and few relevant tools to measure disease activity or prognosis. Here we aimed to assess the predictive performance of liver biochemistry and combined clinical liver scores in a well-characterized population of rPSC.

Methods: All people liver transplanted for primary sclerosing cholangitis in a single center in Oslo, Norway, with at least one serum sample after transplant available in our biobank were included (n=160, 77% male, 82% with concomitant inflammatory bowel disease). A total of 575 serum samples were available from up to 6 time points (median 4). Data on recurrence and clinical course were available from an ongoing study, where available liver biopsies and MRIs post-transplant from the participants were evaluated in a blinded fashion to establish presence and time of recurrent PSC. Other transplantation data were retrieved form the Nordic liver transplant registry. Standard biochemical parameters were retrieved from the hospital lab system and the clinical scores APRI and FIB-4 were generated.

Preliminary results: Median age at listing for liver transplantation was 42 years (IQR 36-63). During follow-up, n=104 (65%) were diagnosed with rPSC, and the median rPSC-free survival after LT was 5.1 years. Three types of analyses were performed: i) A single time point analysis to assess the predictive performance 1 year after transplantation showed no difference between people later developing rPSC or not for any of the parameters. ii) A paired analysis was performed between the last sample before rPSC diagnosis (but >6 months before) and the first sample after to assess diagnostics properties. Only APRI (p=0.01) and FIB-4 (p=0.003) showed a significant increase suggesting a diagnostic value. iii) Finally, all samples taken after rPSC diagnosis were assessed for the ability to predict liver retransplantation-free survival. In time-dependent univariable Cox regressions of log2-transformed variables, FIB-4 (HR 1.7, 95% CI 1.1-2.5, p=0.02), APRI (HR 1.9, 95% CI 1.4-2.6, p = 0.00003), bilirubin (HR 1.5, 95% CI 1.1-2.0, p=0.016) and ALP (HR 2.1, 95% CI 1.4-3.1, p=0.0003) associated with risk of retransplantation or death.

Conclusion/proposal: Biochemical parameters of cholestasis, APRI and FIB-4 predict the outcome of rPSC. To establish a framework for improved care we propose to work together to define clinically relevant biomarkers in rPSC based on standard biochemistry and clinical scores, as well as novel biomarkers based on biobank material.

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Select which of the following topics your abstract belongs to:

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Title of Abstract

36. Serological markers of intestinal barrier function in patients with primary sclerosing cholangitis and inflammatory bowel disease after liver transplantation

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Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background:

Recurrence of primary sclerosing cholangitis (rPSC) is a common long-term complication after liver transplantation (LT), which affect graft survival and overall patient survival. There are several lines of evidence indicating that dysregulation of the microbiome and gut barrier dysfunction are key etiologic factors in the pathogenesis of PSC.

Methods:

The aim of this cross-sectional study was to evaluate serological markers of intestinal barrier permeability in patients with PSC after LT and in control group, to determine potential biomarkers for rPSC. The control group consisted of LT recipients for alcohol-related liver disease and/or hepatocellular carcinoma. The rPSC was assessed by MRCP and/or biopsies, all patients underwent colonoscopy. Serum levels of iFABP, Zonulin and Reg3a were evaluated. Non-parametric tests were used to for initial assessment. We further built generalized linear models for the prediction of PSC diagnosis independent of recurrence, for the prediction of non-rPSC and for the prediction of rPSC using all three permeability markers, BMI and faecal calprotectin as predictors.

Results:

A total of 113 patients were included in the study after LT for PSC and 69 controls. The clinical characteristics of the study participants are listed in Table 1. No significant difference in median of concentrations of Reg3a was found between the PSC group and control group ($p=0.01$). Interestingly, medians of concentrations of iFABP ($p<0.01$) and ($p<0.0001$) Zonulin were significantly higher in the control group in comparison with PSC group. The ROC AUC for Model_1 for prediction of PSC diagnosis per se was 0.79. The increased probability of PSC occurrence was associated with higher Reg3a serum concentration, while a negative relationship was found between the probability of PSC occurrence and BMI, zonulin and iFABP. Model_2, prediction of PSC without recurrence (non-rPSC), achieved slightly better performance, ROC AUC = 0.83, but the predictors and their coefficients and OR were close to Model_1. The ROC AUC for Model_3 predicting rPSC was 0.73. In contrast to previous models, BMI, Reg3A and iFABP were not significantly associated with rPSC, while both higher serum concentrations of zonulin and calprotectin increased the probability of PSC recurrence.

Proposal:

Since the number of patients included in the study is limited and the results are rather subtle, we would like to compare the results of serologic markers of intestinal barrier dysfunction in similar cohort of PSC patients after liver transplantation.

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Recurrent PSC/Liver transplantation

Select which of the following topics your abstract belongs to:

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Title of Abstract

37. The Swedish initiative for the study of Primary sclerosing cholangitis (SUPRIM)

Authors; Name, title (Mark presenting author with *) and Institution (s)
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Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background
Despite more than 50 years of research and parallel improvements in hepatology and oncology, there is still today neither a treatment to prevent disease progression in primary sclerosing cholangitis (PSC), nor reliable early diagnostic tools for the associated hepatobiliary cancers. Importantly, the limited understanding of the underlying biological mechanisms in PSC and its natural history not only affects the identification of new drug targets but implies a lack of surrogate markers that hampers the design of clinical trials and the evaluation of drug efficacy. The lack of easy access to large representative well-characterised prospective resources is an important contributing factor to the current situation.

Methods
We here present the SUPRIM cohort, a national multicentre prospective longitudinal study of unselected PSC patients capturing the representative diversity of PSC phenotypes. We describe the 10-year effort of inclusion and follow-up, an intermediate analysis report including original results, and the associated research resource. All included patients gave written informed consent (recruitment: November 2011–April 2016).

Findings
Out of 512 included patients, 452 patients completed the five-year follow-up without endpoint outcomes. Liver transplantation was performed in 54 patients (10%) and hepatobiliary malignancy was diagnosed in 15 patients (3%). We draw a comprehensive landscape of the multidimensional clinical and biological heterogeneity of PSC illustrating the diversity of PSC phenotypes. Performances of available predictive scores are compared and perspectives on the continuation of the SUPRIM cohort are provided.

Interpretation
We envision the SUPRIM cohort as an open-access collaborative resource to accelerate the generation of new knowledge and independent validations of promising ones with the aim to uncover reliable diagnostics, prognostic tools, surrogate markers, and new treatment targets by 2040.

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Surveillance

Deadline is May 15th, 2024. Write "Proposal for IPSCSG meeting" in the subject line. Send it to annika.roback@regionstockholm.se

Title of Abstract

38. Gallbladder polyps in PSC and rates of malignancy: time for a multicentre study?

Authors; Name, title (Mark presenting author with *) and Institution (s)

Dr Ben Rea*, Miss Samantha Buelu, Miss Sophie Curran, Dr Katie Hoyles, Prof Dermot Gleeson. (Sheffield, UK)

Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background:
Guidelines recommend that patients with Primary Sclerosing Cholangitis (PSC) undergo annual ultrasound (US) surveillance for gallbladder cancer. We aimed to audit the surveillance of our PSC patients and to review the findings and histology of any cholecystectomies.

Methods:
138 patients were identified from our PSC database. Their US surveillance rate between 2012-2022 was assessed against our standard that all patients should have an annual US of the gallbladder (100%). Cross sectional imaging (MRI and CT) was deemed unsuitable for gallbladder surveillance and was excluded. The presence of polyps and their size was noted, and any cholecystectomies and subsequent histology reports were recorded.

Results:
Of the 138 patients only 9.4% (n=13) had regular and complete annual surveillance (one US per calendar year if eligible). The percentage of patients scanned increased from 28% in 2012 to 83% in 2022 (mean=66.1%, median (range) 68% (28%-90 %)). Overall, 41% of eligible scans were performed over the 10-year time span. 7 patients (5%) with polyps were identified via US surveillance (age 27-74, 5 male). Four patients underwent cholecystectomy for polyps: (mean size =17.3mm; media(range) 14.5(10-30mm)). Histology showed adenocarcinoma (n=3) or high-grade dysplasia (n=1) Polyps in three other patients (mean=4.7mm, median(range) 5 (4-7mm)) have not been excised . Cholecystectomies had been performed in 25 additional patients, predomimately as part of liver transplantations (n=14) or for benign pathology such as gallstone disease, and no incidental polyps or dysplasia were found.

Proposal:
Studies on the rates of malignancies within gallbladder polyps are almost always limited to single centre, retrospective, observational studies. Reported values for gallbladder polyp prevalence in patients with PSC have varied, as have recommendations regarding criteria for their removal. We suggest that a multicentre study on this topic would be of benefit for the PSC community, and help inform future practice and guidelines

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Surveillance

Deadline is May 15th, 2024. Write "Proposal for IPSCSG meeting" in the subject line. Send it to annika.roback@regionstockholm.se

Title of Abstract

39. The long-term variability of pruritus in primary sclerosing cholangitis: results of an observational cohort study

Authors; Name, title (Mark presenting author with *) and Institution (s)
Nasir Hussain*, James Ferguson, Nadir Abbas, Usha Gungabissoon, Linda Casillas, Sumanta Mukherjee, Andrea Ribeiro, Martine Walmsley, Paula Harford, Megan McLaughlin and Palak Trivedi (University of Birmingham, GSK, PSC Support)

Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background/Aims: Pruritus is a recognised symptom of primary sclerosing cholangitis (PSC). We conducted a prospective observational clinical trial (ISRCTN:15518794) to capture the burden of pruritus in PSC, including how the temporal variability in symptoms may be used to inform design of future interventional trials.

Methods: Adults with PSC (age >16y; non-transplant) completed health-related quality of life (QoL) assessments (CLDQ and EQ-5D-5L) alongside pruritus questionnaires (the 5D itch score with 2-week symptom recall, and the itch numerical rating scale (NRS) with 24-hour recall). Baseline factors associated with persistent pruritus were identified, and the inherent variability in symptom intensity quantified over time.

Results: Between Jul 21 and Feb 23, 200 PSC pts were recruited (median age 39y, 115 men, median MELD score 7), of whom 100 (50%) reported pruritus of any degree (median 5D itch score was 8.0, IQR 5.0-12.0), consisting of 25 taking anti-pruritic therapy. Baseline 5D itch scores negatively correlated with age ($r = -0.204$, $p = 0.004$), with low-moderate positive correlations against serum ALT ($r = 0.197$, $p = 0.005$), ALP ($r = 0.319$, $p < 0.001$), bilirubin ($r = 0.251$, $p < 0.001$) and bile acid values ($r = 0.354$, $p < 0.001$). Median baseline 5D-itch scores were greater in pts with cirrhosis vs. no cirrhosis (10.5 vs. 6.0), those with transient elastography scores >8.0kPa vs. <8.0kPa (9.0 vs. 5.0) or a history of recurrent acute cholangitis (11.0 vs. 6.0) (all comparisons: $p < 0.001$). Of 31 pts who reported moderate-severe pruritus at baseline (NRS > 4), the majority (61%) reported persistent moderate-severe pruritus at 36-48 weeks. Reciprocally 39% reported improvement to no/mild pruritus (NRS < 3). Amongst pts with an NRS < 3 at baseline (n=118), 11% reported new onset or worsening pruritus to NRS > 4. Cirrhosis was a risk factor for pts developing de novo or worsening pruritus over time (OR 3.75, 95% CI 1.17-12.05). Anti-pruritic therapy did not significantly impact pruritus score from w0 to w36-48. Applying our data to inform the design of a future long-term placebo-controlled trial, using NRS > 4 as an inclusion criterion, and a primary endpoint of NRS < 3 at 48 weeks (1:1 randomisation, two-sided alpha, 80% power); treatment response rates of 60%, 70% and 80%, would require 316, 126 and 64 participants per treatment arm, respectively. Comparatively, a primary endpoint NRS score reduction of < 2 would require 238, 86 and 42 patients per arm, respectively.

Conclusion: Pruritus is common in pts with PSC, and persists over time. It is reported as more intense among pts with advanced disease. Long-term treatment trials will require large pt numbers if powered using conventional, statistical study designs, which is not tenable given the rare nature of PSC.

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Surveillance

Select which of the following topics your abstract belongs to:

Deadline is May 15th, 2024. Write "Proposal for IPSCSG meeting" in the subject line. Send it to annika.roback@regionstockholm.se

Title of Abstract

40. A Protocol for the Development of a Core Outcome Set for Clinical Trials in PSC

Authors; Name, title (Mark presenting author with *) and Institution (s)
Nasir Hussain*(Uni. of Birmingham), Christopher Ma, Gideon M Hirschfield, Mette Vesterhus, Kris Kowdley, Annika Bergquist, Cyriel Ponsioen, Cynthia Levy, David Assis, Christoph Schramm, Christopher Bowlus, Michael Trauner, Olalekan Lee Aiyegbusi, Vipul Jairath and Palak J. Trivedi

Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background:
Primary sclerosing cholangitis (PSC) is a progressive immune mediated liver disease, for which no medical therapy has been shown to slow disease progression. However, the horizon for new therapies is encouraging, with several innovative clinical trials in progress. Despite these advancements, there is considerable heterogeneity in the outcomes studied, with lack of consensus as to what outcomes to measure, when to measure, and how to measure. Furthermore, there has been a paradigm shift in PSC treatment targets over recent years, moving from biochemistry-based endpoints to histological assessment of liver fibrosis, imaging-based biomarkers, and patient reported outcome measures. The abundance of new interventional trials and evolving endpoints pose opportunities for all stakeholders involved in evaluating novel therapies. To this effect, there is need to harmonise measures used in clinical trials through the development of a core outcome set (COS).

Methods and Analysis:
Synthesis of a PSC-specific COS will be conducted in four stages. Initially, a systematic literature review will be performed to identify outcomes previously used in PSC trials, followed by semi-structured qualitative interviews conducted with key stakeholders. The latter may include patients, clinicians, researchers, pharmaceutical industry representatives, and healthcare payers and regulatory agencies, to identify additional outcomes of importance. Using the outcomes generated from literature review and stakeholder interviews, an international two-round Delphi survey will be conducted to prioritise outcomes for inclusion in the COS. Finally, a consensus meeting will be convened to ratify the COS and disseminate findings for application in future PSC trials.

Ethics and dissemination:
Ethical approval has been sought with respect to patient participation. The core outcome set from this study will be widely disseminated including publication in peer-reviewed journals, international conferences, promotion through patient-support-groups and made available on the COMET database

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Select which of the following topics your abstract belongs to:

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Title of Abstract

41. Continued Development and International Validation of the Provisional UK-PSC-QoL Tool.

Authors; Name, title (Mark presenting author with *) and Institution (s)
Ryan James, Mr* (University of Hertfordshire), Emily Beadle, Dr (University of Hertfordshire), Douglas Thorburn, Dr (Sheila Sherlock Liver Centre & UCL Institute for Liver & Digestive Health, London, UK), Shivani Sharma, Dr (Aston University).

Body text (background/rational, methods, preliminary results, what you ask for- your proposal)

Background/ rational: Quality of Life (QoL) is an important dimension of patient care. Measurement of QoL can help shape health policy, clinical practice, and intervention evaluation. Several self-complete QoL assessment tools are available, though in the context of Primary Sclerosing Cholangitis (PSC), they may lack sensitivity to detect condition specific issues that matter to patients. Development of a PSC specific QoL is therefore advantageous.

Based on an initial review of relevant literature, our UK based team undertook preliminary work to develop a PSC QoL. After qualitative inquiry with adult patients and health care professionals, 83 items were generated including a 6-item stand-alone Stoma 'Module'.

Aims: Current research focuses on refinement of the tool to yield a brief but rigorous measure for use in everyday care and research. Development work will include cross cultural validation to extend reach and impact through parentship with other research teams and regulators. Our aim here is to describe learning from scale development to date, and to outline and gain expert feedback on the next planned phases. This will include further refinement of items drawing on international patient perspectives, and wider scale testing of the tool for comprehension, usability, and psychometric properties to provide confidence that the QoL tool meets its intended aims in a consistent way.

Our researcher team is also planning an ERN workshop for early 2025. Along with iPSCSG, this will help to establish stakeholder needs, further consult experts, facilitate discussions, foster collaborations, coordinate initiatives and engage with regulators and PSC healthcare networks.

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Surveillance