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PHD THESIS

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Current standard and prospects for diagnosis and monitoring of patients with primary sclerosing cholangitis with the aim of improving prognosis

PHD THESIS SUMMARY

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Summary

I. General Part

1. Current state of knowledge

Primary sclerosing cholangitis (PSC) is an immune-mediated liver disease that affects the bile ducts and progresses to liver cirrhosis and its complications, which can lead to cholangiocarcinoma (CCA). It occurs with the formation of strictures in the small or large bile ducts, associated with cholestasis. The disease is localized to the liver but can be focal, leaving unaffected areas. Currently, PSC is one of the most challenging liver diseases in terms of diagnosis and management, with no known etiology, mode of progression, or effective treatment (1).

PSC can be associated with other immune-mediated conditions, the most important being Inflammatory Bowel Disease (IBD). Both Crohn's Disease (CD) and Ulcerative Colitis (UC) can be associated with PSC, most frequently at the time of diagnosis of one of them (PSC or IBD), but they can also occur independently.

Depending on age and sex, the patient with PSC-IBD is usually male and with an age of 30 to 40 years at diagnosis of PSC (2,3). UC is the predominant type of IBD associated with PSC, with the association reported in up to 85% of cases, especially in countries where the association between CSP and IBD is more common (2).

Liver transplantation in PSC is the only type of therapy considered curative. Post-liver transplant PSC recurrence (rPSC) occurs in 10-37% of transplant patients (4,5).

Suppose the autoimmune disease that overlaps with the underlying one affects the same organ and shows overlapping histological, immunological, and serological changes. In that case, the condition is called "variant syndrome" (VS), the preferred term to define the overlap between PSC and Autoimmune Hepatitis (AIH) or Primary Biliary Cholangitis (PBC) (1,6,7).

Periodic surveillance of patients with PSC involves a multidisciplinary approach and is a way to improve prognosis by detecting complications at early stages, when options for resolution are greater. The most important complications are CCA, followed by progression of stenosis and liver fibrosis (4,5,8).

2. Monitoring of patients with Primary Sclerosing Cholangitis

2.1. Prognostic scores for patient monitoring and stratification

In order to stratify patients and predict the prognosis of PSC cases, several prognostic scores were developed. Scores are based on clinical, paraclinical, and imaging parameters (9). The most commonly used clinical outcomes are: overall survival, survival without liver transplantation, liver-related death, liver transplantation, liver cirrhosis, or bacterial cholangitis (10). For use in clinical research, as a primary or secondary outcome, the 2016 IPSCSG consensus recommended considering composite clinical outcomes that have a similar long-term impact (11).

The Mayo Risk Score (MRS) assesses short-term mortality and liver transplant risk. The Amsterdam Oxford Model (AOM) predicts survival without transplantation or death. The PREsTo score estimates the risk of liver decompensation and the need for transplantation. The UK-PSC dynamic score predicts the risk of liver-related death or transplantation (10).

Imaging scores are prognostic scores derived from MRCP exams used to predict disease progression. They correlate with clinical scores and are developed as prognostic biomarkers. (12). *The Majoie classification* was initially described for Endoscopic Retrograde Cholangio-Pancreatography (ERCP) and later validated by Ponsioen et al. (13,14) . It was subsequently adapted for MRCP examinations and validated on a pediatric population by Patil et al. It evaluates strictures in the intrahepatic and extrahepatic bile ducts (15).

2.2. Medical education of patients and health literacy

Medical education and health literacy is the degree of information, understanding and knowledge of the basic information necessary for an individual to make decisions about personal health, as specified by the World Health Organization (WHO) (16,17). Currently, it is more discussed under the name of eHealth Literacy, referring to digital materials that provide medical information and the ability of the individual to understand and critically evaluate this information for solving health problems (18). For patients with PSC or PBC, it is an additional challenge, given that information about the two diseases is limited (19,20).

II. Original part

3. Working hypothesis and general objectives

The PhD thesis entitled "Current standard and prospects for diagnosis and monitoring of patients with primary sclerosing cholangitis with the aim of improving prognosis" aimed to evaluate the current state of evaluation and diagnosis of patients with PSC in a tertiary hepatology center in Romania and to evaluate the options for monitoring and stratification of patients by using prognostic scores, but also to improve patients' prognosis by increasing patients' access to medical education.

A. Establishing the profile of patients diagnosed with PSC, the diagnosis method, and the management methods used, with the evaluation of the occurrence of complications.
B. Usefulness of clinical and imaging scores in determining the prognosis of patients with PSC
C. Determination of the impact of PSC on patients with IBD and the relevance of enzyme cholestasis syndrome in the diagnosis of liver diseases in these patients
D. Improving patients' quality of life by increasing access to health literacy.

4. General working methods and analysis.

4.1. Statistical data analysis

Statistical analyses were performed with GraphPad Prism, MedCalc v22 and DataTAB. The continuous variables were expressed as means (95%CI, SD) or IQR, and the categorical variables as frequencies. The following were used: t-test for normal distributions, Mann–Whitney U for nonparametric distributions, and χ^2/Fisher for categorical variables. The performance of the variables was evaluated by ROC curves (AUROC). Independent factors were identified by multivariate logistic regression (R^2 Nagelkerke). Time-event analysis used Cox regression and Kaplan–Meier curves. Significance threshold: $p < 0.05$.

5. Evaluation of the usefulness of clinical prognostic and imaging scores within the cohort of patients diagnosed with PSC

5.1. Introduction (working hypothesis and specific objectives)

The role of this study was to evaluate the cohort of patients diagnosed in the Fundeni Clinical Institute, in order to establish the profile of patients and the complications that occurred, and the usefulness of clinical scores, treatment response criteria, and one of the imaging scores for assessing the prognosis of patients (21).

5.2. Materials and Methods

This is a retrospective single-center study conducted at the Fundeni Clinical Institute, Bucharest. It included 145 patients diagnosed with PSC by MRCP examination and/or liver biopsy, after excluding other causes of PSC. The study included patients evaluated between June 2011 and June 2025.

5.3. Results

The average monitoring period was 62.35 months (IQR 18-99), totaling 9041 months (753.41 cumulative years of monitoring). Statistically significant differences were observed between patients who underwent liver transplantation, decompensated liver cirrhosis being the most frequent indication ($p<0.001$), but also 7.92% of patients without liver cirrhosis underwent LT, emphasizing the specific indications of PSC. Statistically significant differences were observed in Metabolic bone disease (12.94% vs 1.67%, $p=0.015$) and thyroid disease (14.12% vs 1.67%, $p=0.01$) compared to males.

The analysis of the OLTDECN composite clinical outcome and the clinical scores AOM, MRS, PREsTo, and MELD-Na (and the newer variant, MELD 3.0), shows that there are significant differences between the groups that presented PSC-associated events ($p<0.05$), for AOM, MRS, MELD-Na, and MELD 3.0, but not for the PREsTo score.

The response to UDCA at 12 months, according to the Paris II criteria (adapted from the PBC study), showed that 41.4% of patients improved on the tests at 12 months of treatment (22). 55.2% showed a decrease in MRS score and 40.2% in AOM score.

The analysis of MRCP imaging scores based on the Majoie classification was performed in a subgroup of 64 patients who had at least 2 MRCP examinations, evaluated between 2011 and 2022 (23).

Comparative predictability analysis of clinical outcomes was performed using AUROC to compare clinical and imaging scores. The MRS score had an AUROC of 0.936 for OLTDECN, UKPSC, 0.893, while the CBIH imaging score had 0.665, and the CBIH+CBEH sum score of 0.625.

Harrell's C-statistic concordance analysis of imaging scores calculated from MRCP images using the Majoie classification shows good concordance between the CBIH score and the clinical outcome of THDEC (c-statistic 0.780), as well as between the CBIH+CBEH sum score and the clinical outcome of THDEC (c-statistic 0.697).

We also performed a logistic regression analysis using the APRI and CBIH scores to develop a model for composite clinical outcomes (OLTDECN and THDEC). The model ($p=0.0001$) and each variable were statistically significant ($p<0.05$), for both clinical outcomes, AUROC = 0.821 (ES = 0.05) for OLTDECN and 0.813 (ES 0.05) for THDEC, respectively.

5.4. Conclusions

The study shows that the population of patients with PSC in a Romanian tertiary hepatology center has specific demographic characteristics, a lower association with IBD, a long-term course, and associations with variant syndromes, including AIH and PBC.

We validated the clinical and imaging prognostic scores based on the Majoie classification of lesions from the MRCP exams, with variable performance, the best being MRS, UK-PSC, and MELD 3.0. The PREsTo and AOM scores performed worse. A combined score with the classification of intrahepatic bile duct lesions and the APRI fibrosis score is effective in identifying patients at risk for liver events, surpassing the classic scores for liver transplantation. The response to UDCA treatment indicates the usefulness of reducing the MRS score as a target, and the other criteria taken from the PBC studies included fewer patients than in the specific studies.

6. Evaluation of the association of Primary Sclerosing Cholangitis with Inflammatory Bowel Diseases and the Importance of Enzymatic Cholestasis Syndrome for the Diagnosis of Liver Disease

6.1. Introduction (working hypothesis and specific objectives)

PSC has a close relationship with IBD in terms of pathophysiology, clinical features, epidemiology, and long-term evolution. This study had the following objectives: to evaluate the association between IBD and PSC, in terms of disease severity and phenotype; and to evaluate biochemical cholestasis in patients with inflammatory bowel disease for the diagnosis of liver disease.

6.2. Materials and methods

This study included patients evaluated at a single medical center, Fundeni Clinical Institute, in Bucharest, evaluated between September 2011 and September 2022, for a diagnosis of IBD. A total of 3767 patients were included.

6.3. Results

2502 patients were diagnosed with an IBD, 1.35% of patients were diagnosed with PSC. A younger age at diagnosis was observed for patients with PSC-IBD, a higher rate of diagnosis of CCA than the population without PSC, and a higher mortality rate. There were statistically significant differences in the need for biological treatment in patients with CD (60% in CD-PSC vs. 15.7% in UC-PSC, $p=0.001$), who also had a higher rate of severe IBD (73.3% vs. 10.5%, $p<0.001$), but also a lower mean age at diagnosis of PSC, compared to UC-PSC (31.53 vs. 40.37, $p=0.005$).

Of the total patients, 13.3% had enzymatic cholestasis syndrome. Of these, 44.14% were diagnosed with a liver disease, representing 5.88% of all patients with IBD. MASLD was more commonly diagnosed in patients with CD ($p=0.009$). The predictive capacity of the cholestasis enzymes GGT and ALP for PSC was 0.938 (SE = 0.02) for ALP and 0.892 (SE = 0.03) for GGT, respectively, with no significant difference between the two ($p = 0.064$).

6.4. Conclusions

The study looked at the association between IBD and PSC and the role of cholestasis enzymes in diagnosing liver disease. The prevalence of PSC in IBD is similar between UC and CD, at 1.37% and 1.34%, lower than in other studies. Cholestasis markers are independent predictive factors, with higher values in patients with liver disease.

7. Improving the prognosis and quality of life of patients with Primary Sclerosing Cholangitis and Primary Biliary Cholangitis by increasing access to medical education, community and medical services

7.1. Introduction (working hypothesis and specific objectives)

Immune-mediated cholestatic diseases, PSC and PBC are two rare hepatobiliary disorders, with an uncertain prognosis in the absence of treatment, but also of effective monitoring, given the risk of complications. The need for medical information and education among the population is a health problem. Access to medical interaction, medical assessments and community of patients affected by the disease can improve the quality of life by developing individual coping methods(16,24).

This study aimed to present the methodology for developing and implementing an online platform that would provide patients with access to medical information, improve medical literacy, and foster a community of patients. One objective was to assess the patients' quality of life (QoL) and the usefulness of the online platform.

7.2. Materials and methods

An online platform was created for patients diagnosed with PSC, PBC, or AIH, based on other platforms dedicated to patients in other countries (France, UK, USA). The online platform allows patients to be registered and collect a minimum set of diagnostic data. The data is verified by the doctors involved in this project, who evaluate the patients. The medical information is based on the EASL and AASLD guidelines, translated into Romanian and adapted to be in a common, easy-to-understand language. The information on the site is general and covers diagnosis, epidemiology, monitoring, treatment, nutritional aspects, and physical activity (4,5,25,26).

The online platform www.colangite.ro fulfills several roles: educational, patient community, patient registration, and facilitation of the partnership between patients and doctors.

To evaluate the online platform, a non-standard questionnaire on the quality and impact on lifestyle, as well as the clarity of the information, was administered. The period in which the questionnaire was distributed and the collected responses were between June 25, 2025, and July 1, 2025, during which a total of 33 people responded.

To measure quality of life, the *PBC-10* questionnaire for patients with PBC and the *CLDQ-PSC* questionnaire for those with PSC was used. They were administered in a pilot study to assess the feasibility of online administration, without validation.

7.3. Results

Since the launch of the online platform on March 29, 2023, and through August 1, 2025, 81 patients from across the country have registered. Of these, most have a diagnosis of PBC, followed by those with PSC and those with AIH. Most registered members are female (87%) and from urban areas (71.43%), with an average age at diagnosis of 44.47 years.

To evaluate the online platform and its usefulness, we administered 3 questionnaires to enrolled patients. The purpose of conducting these questionnaires was to see if the degree of use and satisfaction of patients can also be applied.

The first questionnaire applied is regarding access to the online platform. 82.4% of patients considered medical literacy a public health issue. All respondents considered that medical education should be included in everyone's education. Regarding medical literacy, patients' responses improved after using the online platform.

The PSC QOL questionnaire showed that fatigue and sleep impairment are the most important symptoms. In PBC, fatigue has been reported to have a significant impact on the degree of alteration in quality of life (20).

7.4. Conclusions

This study provides a comprehensive overview of the methodology for developing and implementing a digital platform specifically designed for patients diagnosed with PSC and PBC. It is noteworthy that this platform is, in particular, the first online resource in Romania to focus on improving patient health literacy and doctor-patient interactions. The platform's main target audience was the urban population with access to digital technology and educational resources. Recognizing the diverse needs of patients, the platform also offers printed educational materials to ensure accessibility for people with limited digital literacy or internet access.

8. General conclusions and Personal contributions

8.1. General conclusions

The main purpose of this paper was to present an evaluation of patients diagnosed with Primary Sclerosing Cholangitis in a gastroenterology center in Romania, presenting data on epidemiology, diagnosis, and long-term evolution, using current methods. It aimed to improve prognosis by increasing access to information and specialized services and by fostering community. This PhD thesis is one of the first of its kind to evaluate patients with PSC in Romania, both in line with current standards and by introducing a method to improve prognosis.

The validation of the clinical prognostic scores in the Romanian population was performed, and the phenotypic peculiarities were described. The utility of imaging scores from the Majoie classification was confirmed in adults. Patients were found to respond inadequately to UDCA, with only partial improvement in cholestasis enzymes.

The study on the association between PSC and IBD shows that PSC is one of the most commonly associated liver diseases with IBD, and has a lower prevalence than expected. The association with UC is more common, but CD is more severe.

The research led to the establishment of the first online platform for patients with PSC and PBC in Romania, providing validated medical education to improve literacy and monitoring.

8.2. Personal contributions

One contribution was to develop the study design for the research. We collected data from medical registries for retrospective studies and calculated the prognostic clinical scores. We developed, established, and financed the online platform by handling the IT and administrative components and its content. Together with the scientific coordinator, we developed the content of the patient information materials, which were later published online and in the brochures given to patients.

Together with the collaborating graphic designer, we made the explanatory images and the design of the informative materials. I have contributed to patient interactions through the online platform we manage, from which I have collected the data.

I performed statistical analysis of the data and wrote the published scientific articles.

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