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Prognostic Models of Primary Sclerosing Cholangitis

Anastasia I. Dolgushina[1], Anna A. Selyanina[1,*], Viktoria V. Dubrovina[1], Gulnaz A. Isyangildina[1], Elena R. Olevskaya[1,2]

[1] *South Ural State Medical University, Chelyabinsk, Russian Federation*
[2] *Chelyabinsk Regional Clinical Hospital, Chelyabinsk, Russian Federation*

Aim: to study the significance of prognostic scales in a target group of patients with primary sclerosing cholangitis (PSC) living in the Chelyabinsk region.
Materials and methods. The study included 21 patients with a confirmed diagnosis of primary sclerosing cholangitis (PSC) and a disease duration of at least two years. The primary endpoint studied was death. The MELD, Mayo Risk Score, Amsterdam-Oxford PSC Score, PREsTo score, and UK-PSC Score scales were calculated based on the medical records. Statistical processing was carried out using the SPSS Statistics v.22 application.
Results. A retrospective assessment of the risk of mortality using the MELD, Mayo Risk Score and Amsterdam-Oxford PSC Score did not reveal a statistically significant difference between deceased and surviving patients. The UK-PSC Score scale showed the highest predictive value ($p = 0.046$).
Conclusion. The new predictive model UK-PSC Score showed advantages in predicting death in PSC patients compared to other scales.
Keywords: primary sclerosing cholangitis, new prognostic models, prognosis, survival, liver cirrhosis

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Прогностические модели первичного склерозирующего холангита

А.И. Долгушина[1], А.А. Селянина[1,*], В.В. Дубровина[1], Г.А. Исянгильдина[1], Е.Р. Олевская[1,2]
[1] *ФГБОУ ВО «Южно-Уральский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Челябинск, Российская Федерация*
[2] *ГБУЗ «Челябинская областная клиническая больница», Челябинск, Российская Федерация*

Цель исследования: Изучить значимость прогностических шкал на когорте пациентов с первичным склерозирующим холангитом, проживающих в Челябинской области.
Материалы и методы. В исследование включен 21 пациент с подтвержденным диагнозом первичного склерозирующего холангита (ПСХ) и длительностью заболевания не менее двух лет. Исследуемой первичной конечной точкой являлся летальный исход. На основании данных медицинских карт производили расчет шкалы MELD, Mayo Risk Score, Amsterdam-Oxford PSC Score, PREsTo score и UK-PSC Score. Статистическая обработка проводилась при помощи программы SPSS Statistics v.22.
Результаты. Ретроспективная оценка риска летальности по шкале MELD, Mayo Risk Score и Amsterdam-Oxford PSC Score не выявила статистически значимой разницы между умершими и выжившими пациентами. Наибольшую прогностическую ценность показала шкала UK-PSC Score ($p = 0,046$).
Заключение. Новая прогностическая модель UK-PSC Score показала преимущества в прогнозировании летального исхода у пациентов ПСХ по сравнению с другими шкалами.
Ключевые слова: первичный склерозирующий холангит, новые прогностические модели, прогноз, выживаемость, цирроз печени
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Introduction

Primary sclerosing cholangitis (PSC) is a chronic immune-mediated disease characterized by inflammation, fibrosis, and destruction of the intra- and/or extrahepatic bile ducts, leading to cholestasis, the formation of biliary strictures, and liver fibrosis [1–3]. Despite the fact that the pathogenesis of PSC is not fully understood, a large number of studies confirm the existence of a genetic predisposition to this disease [4]. The characteristic association of PSC and inflammatory bowel disease (IBD) became the basis for the formation of pathogenetic concepts in which the induction and maintenance of inflammation in the biliary tract are associated with the translocation of bacterial products (components of the bacterial cell wall, peptides) due to increased intestinal permeability, and the homing of T-lymphocytes, activated in the intestine, into the bile ducts. Data have been accumulated in addition, on the role of disturbances in bile homeostasis [5].

With a relative rarity of the disease, from 0.5 to 6 per 100,000 inhabitants [6, 7], the course of PSC is associated with a high incidence of adverse outcomes: malignant neoplasms of the biliary tract, liver, pancreas, colorectal cancer (CRC), the development of biliary cirrhosis and the need for liver transplantation [8, 9]. Previous studies have shown that oncological diseases were the cause of death in 44 %, decompensation of liver pathology in 37 % of cases [10]. According to J.J. Tischendorf et al. cholangiocarcinoma accounts for 58 %, while 30 % and 9 % of patients die from liver failure and bleeding from esophageal varices, respectively in the structure of mortality in patients with PSC [11]. According to an analysis of the database of transplant centers in the Netherlands, published in 2013, the most common cause of death in patients with PSC is cholangiocarcinoma (32 %), among other causes of death are liver failure (15 %), post-transplant complications (9 %) and CRC (8 %) [6,7]. According to a multicenter retrospective study conducted in Europe, North America, Australia, in the period from 1980 to 2010 and included 7121 patients, tumors of the hepatobiliary system were diagnosed in 10.9 % of PSC cases. The risk of cholangiocarcinoma, which was the most common neoplasm, increased with age. Overall, adverse events were less common in patients with small duct PSC and women. Patients with ulcerative colitis (UC) had a higher risk of liver disease progression compared with patients with Crohn's disease (relative risk (RR) 1.56; $p < 0.001$) or without IBD (RR 1.15; $p = 0.002$) [12]. In a large population-based study in England conducted between 2006 and 2016, which included 284,560 patients with IBD, of whom 2588 had PSC, patients with a combination of IBD and PSC had a higher risk of death (RR 3.20; $p < 0.001$). Unfavorable prognostic factors were age at diagnosis under 40, Afro-Caribbean race and male gender. PSC increased the risk of cholangiocarcinoma (RR 28.46), hepatocellular carcinoma (RR 21.00), pancreatic cancer (RR 5.26), and gallbladder cancer (RR 9.19) ($p < 0.001$ for all). According to this study, patients with a combination of IBD and PSC also showed an increased risk of CRC (RR 2.43; $p < 0.001$) and an earlier age of developing CRC (59 years vs 69 years old without PSC, $p < 0.001$) [13].

Data obtained from observational studies contributed to the search for various markers with predictive value for PSC (Table 1). The finding that a decrease in alkaline phosphatase (ALP) with ursodeoxycholic acid (UDCA) can predict outcomes in primary biliary cholangitis [14] inspired a study of this parameter in patients with PSC. Studies have shown no significant difference in long-term prognosis between PSC patients treated with UDCA (17–23 mg/kg/day) or placebo. Despite this, patients with lower levels of ALP had a higher life expectancy and a lower risk of developing cholangiocarcinoma, regardless of UDCA treatment [15,16]. A retrospective study conducted in the UK (2019) showed that in patients with PSC, a 2.4-fold increase in ALP was associated with a decrease in 10-year survival [17]. Currently, the search for other laboratory markers is underway, including proteomic analysis of bile from patients with PSC, cholangiocarcinoma in comparison with healthy individuals [18].

The data of various visualization methods were considered as parameters of the prognostic models. In a retrospective study, splenomegaly (greater than 120 mm) is associated with adverse outcomes in patients with PSC [22]. Whereas typical cholangiographic changes determine the diagnosis of PSC, some prognostic scoring systems included bile duct characteristics. In general, the presence of a dominant stricture according to ERCP data naturally worsened survival, and endoscopic treatment improved the prognosis in this situation [23]. Currently, the risk of complications of diagnostic ERCP reduces its applicability in clinical practice. Attempts to incorporate various magnetic resonance imaging (MRI) features of cholangiopathy into PSC prognostic models have led to conflicting results [24].

Determining the stage of liver fibrosis plays a key role in assessing the prognosis for chronic liver diseases of any etiology [25]. Histological examination of the liver tissue with Ludwig staging is the standard for diagnosing fibrosis in PSC, allowing to assess the further progression of the disease. The Enhanced Liver Fibrosis panel of direct biochemical markers of fibrosis deserves special attention among the non-invasive tests for assessing fibrosis (Table 2). Transient elastography measures of liver stiffness in a model of predictors of death and liver transplantation have been studied in a large target group of patients [26]. Magnetic resonance spectrography, as a highly sensitive method for assessing fibrosis, also has prospects for inclusion in PSC prognosis models, but the high cost and low availability limit the use of this method [27]. With the development

Table 1. Association of laboratory markers with PSC prognosis

Indicator	Characteristic changes	Relationship with forecast
ALP	Decreased < 1.5 ULN within 2 years [14]; by 40 % of baseline within 1 year [16]	Factors associated with better survival
	2.4-fold increase in ALP levels	Decreased 10-year survival rate [17]
Bilirubin	Increased bilirubin for more than 3 months	Associated with worse prognosis, this indicator is included in almost all prognostic scales
Albumin	Decrease is a sign of liver failure	Included in many prognostic scales, sensitivity is low in the early stages of the disease
Anti-GP2	Presence of pancreatic autoantibodies	Possible association with cholangiocarcinoma [19]
IL-8	Increase in bile and blood serum	Showed association with PSC severity and poor prognosis [20]
Vap-1	Increased expression in the liver tissue of patients with PSC	An association with clinical outcomes of PSC was observed in two independent groups of patients in one study [21]

Note: ALP — alkaline phosphatase, ULN — upper limit of normal, Anti-GP2 — antibodies to glycoprotein 2 (GP2) of pancreatic centroacinar cells, IL-8 — interleukin 8, Vap-1 — vascular adhesion protein-1.

of liver cirrhosis (LC), the 7-year survival rate of patients with PSC, depending on Child-Pugh class A, B, and C, is 90 % at 68 % and 25 %, respectively [12]. Modern guidelines recommend that in PSC, as in cirrhosis of another etiology, focus on the MELD (Model for Endstage Liver Disease) indicator to determine the timing of liver transplantation [1–3]. Meanwhile heterogeneity of the population of patients with PSC, the high probability of adverse outcomes, in addition to cirrhosis decompensation, leads to the search for new prognostic tools [28].

Mayo Risk Score and revised Mayo Risk Score

The first survival model for PSC patients was developed by the Mayo Clinic and published in 1989. It originally included 5 variables: age, bilirubin level, histological stage, hemoglobin, and presence of IBD. Subsequently, this model was modified (King's College model, multicenter model), refined and studied on a target group of 305 patients from Sweden. The Mayo Risk Assessment (or Nordic Model) published in 1996 included 4 variables: age, bilirubin level, histological stage, and splenomegaly. The need for a liver biopsy significantly limited the use of this prognostic formula, and therefore the revised Mayo Risk Score (rMRS) was published in 2000, which lacks histological stage and subjective variables. A study including 405 patients with PSC revealed comparable accuracy of rMRS with the original model [29]. One of the main drawbacks of rMRS, which has required the development of other predictive models, is the estimation of all-cause mortality, without the ability to predict the time to liver transplantation and other clinically relevant endpoints.

Amsterdam-Oxford PSC Score

The model was developed on a target group of 692 patients with PSC, including a combination of PSC and autoimmune hepatitis (AIH), and validated on 264 patients. The endpoints were death or liver transplantation. The calculation was made on the basis of seven variables, a feature of the model was the inclusion of PSC subtypes: small or large ducts. It should be noted that a small number of patients with small duct PSC were included in the study [30].

Enhanced Liver Fibrosis (ELF)

ELF is a non-invasive test that evaluates three markers of serum hepatic matrix metabolism that are expressed early in fibrogenesis: hyaluronic acid, tissue inhibitor of metalloproteinase-1 (TIMP-1), procollagen III N-terminal peptide (P3NP). Higher ELF values were noted in patients with PSC (305 patients with PSC of large ducts) than in patients with UC and healthy individuals, and are also associated with poor survival [31]. Interestingly, an increase in ELF > 9.8 was noted in cholangiocarcinoma, including those without PSC (RR 4.91 (95 % CI 1.19–20.21) [32].

UK-PSC Score

In 2019, the results of a new risk assessment scale were published in 1001 patients from UK transplant centers. The authors presented two models: for short-term and long-term forecast. At the same time, in the model for 10-year survival, the data (Table 2) obtained in dynamics after 2 years of observation are used. A feature of this study was the parallel study of genetic markers, however, when they were included in the model, no increase in its prognostic value was obtained, and

therefore they were not included in the final version of the UK-PSC Score [17].

PREsTo score

The latest proposed model is the PREsTo scale (Primary Sclerosing Cholangitis Risk Estimate Tool). Its peculiarity is the development and selection of variables using a computer program, the use of CP decompensation as an end point and strict inclusion criteria. Patients with PSC of small ducts, combined with AIH, patients with MELD index > 14 points and/or portal hypertension were excluded. The target group included 787 patients with a 6 years observation term, the validation target group included 278 patients from centers in North America and Norway with a mean follow-up of 4.21 years [33]. A review was published in 2021 comparing predictive models of PSC [28]. The authors note the difficulty of comparing prognostic scales due to different endpoints, time horizons, and inclusion criteria in the study. However, all models were comparable to rMRS and had good statistical performance. The review highlights the need for further research and model validation in various PSC patient populations.

Purpose of the study: To study the significance of prognostic scales in a target group of patients with PSC living in the Chelyabinsk region.

Materiales and methods

A retrospective study was conducted between 2019 and 2021 that included patients with a confirmed diagnosis of PSC and a disease duration of at least two years. The study included 21 patients, including 14 (66.7 %) men and 7 (33.3 %) women. PSC was diagnosed in accordance with current clinical guidelines [1–3]. The primary endpoint studied was death. The MELD scale, Mayo Risk Score, Amsterdam-Oxford PSC Score, PREsTo score were calculated based on the data of medical records in the period two years before inclusion in the study or death. Laboratory results obtained at diagnosis as required for the use of the UK-PSC Score, and one year after diagnosis were taken into account. Statistical processing was carried out using the SPSS Statistics v.22 program. Qualitative data are presented as frequencies and proportions, quantitative data as median and interquartile range. Fisher's exact test was used to compare qualitative indicators, the statistical significance of the difference in quantitative data was analyzed using the Mann–Whitney *U*-test.

Results and discussion

General characteristics of patients at the time of inclusion in the study are presented in Table 3. During a median follow-up period of 48 (34.8–72) months, 3 (14.3 %) patients reached the study primary endpoint (death). The causes of death in two patients were liver failure (follow-up period 60 and 204 months) and in one patient CRC (follow-up period 24 months).

A level above 14 points was taken as a high risk of death on the MELD scale while calculating prognostic indicators [3]. Mortality risk assessment on the MELD scale did not reveal a statistically significant difference

Table 2. PSC predictive models

Model	Variables	End points and time period	Link to calculator
Mayo risk score (rMRS)	Age, total bilirubin, AST, bleeding from esophageal varices, albumin	4-year overall survival estimate	www.psc-literature.org/mrscalc.htm
Amsterdam-Oxford PSC Score	PSC subtype, age at diagnosis, albumin, platelets, AST, ALP, bilirubin	1-year transplant-free survival;	sorted.co/psc-calculator
Enhanced Liver Fibrosis (ELF)	Hyaluronic acid, TIMP-1, P3NP	5-, 10- and 15-year prognosis available	–
UK-PSC Score	Short-term risk: bilirubin, albumin, hemoglobin and platelets	Death or liver transplant within 4 and 10 years	www.uk-psc.com/resources/the-uk-psc-risk-scores
	Long-term risk: age at diagnosis, bilirubin, alkaline phosphatase, platelets, extrahepatic duct injury, bleeding from esophageal varices	2-year transplant-free survival	
Primary Sclerosing Cholangitis Risk Estimate Tool (PREsTo score)	Bilirubin, albumin, alkaline phosphatase, platelets, AST, hemoglobin, sodium, patient age and years since PSC diagnosis	10-year transplant-free survival	rtools.mayo.edu/PRESTO_calculator
		1–5 year to hepatic decompensation	

Note: AST — aspartate aminotransferase, PSC — primary sclerosing cholangitis, ALP — alkaline phosphatase, TIMP-1 — tissue inhibitor of metalloproteinase-1, P3NP — procollagen III N-terminal peptide.

Table 3. Characteristics of PSC patients included in the study

Parameter	Patients with PSC, *n* = 21
Gender (m/f), *n* (%)	14 (66.7) / 7 (33.3)
Age at the time of diagnosis, years), years, Me (IR)	40.5 (26.0; 51.5)
Smoking, *n* (%)	2 (9.5)
Combination of PSC and IgG4-associated cholangitis, *n* (%)	1 (4.8)
Combination of PSC and autoimmune hepatitis, *n* (%)	3 (14.3)
PSC of small ducts, *n* (%)	8 (38.1)
PSC of large ducts, *n* (%)	13 (61.9)
Ulcerative colitis, *n* (%)	19 (90.5)
Liver cirrhosis, *n* (%)	6 (28.6)
Liver cirrhosis Child-Pugh class A, *n* (%)	4 (19)
Liver cirrhosis Child-Pugh class B, *n* (%)	1(4.8)
Liver cirrhosis Child-Pugh class C, *n* (%)	1(4.8)

Note: PSC — primary sclerosing cholangitis.

(p = 0.386) in the compared groups (Table 4). We did not record a high Mayo Risk Score in any of the deceased patients. A high risk of death according to the Amsterdam-Oxford PSC Score was established at an index value of more than 2; when analyzing the calculation of this indicator in the study group of patients, a trend was found towards a more frequent occurrence of a high risk of death among deceased patients, however, this difference did not reach statistical significance (p = 0.140). The scale that showed the highest predictive value was the UK-PSC Score, according to the results of which a high risk of death was established at a value of the indicator above –0.8146346 (p = 0.046). 7 (35 %) patients met the inclusion criteria for calculating the risk of cirrhosis decompensation according to the PREsTo score scale, the median probability of cirrhosis decompensation was higher in the group of deceased patients, but due to a small sample, this indicator was not significant.

Discussion

Currently, the main prognostic indicator that is used to determine the order of placing a patient on a waiting list for liver transplantation, regardless of the etiology

Table 4. Comparative characteristics of the prognostic scales calculation results analysis in patients with PSC

Parameter	PSC patients who died during follow-up, *n* = 3 (14.3 %)	PSC patients who survived during follow-up, *n* = 18 (85.7 %)	*p*
MELD			
More than 14 points on the MELD scale, *n* (%)	1 (33.3)	2 (11.1)	0.386
rMRS			
High risk of death according to rMRS, *n* (%)	0	1 (5.6)	-
UK-PSC Score			
Высокий риск летального исхода по шкале UK-PSC Score, *n* (%)	2 (66.7)	1 (5.6)	0.046*
PREsTo score*			
Risk of cirrhosis decompensation within 1 year according to the PREsTo scale, %	2.2 (2.2; 2.2)	0.8 (0.5; 1.5)	0.143
Risk of cirrhosis decompensation within 5 years according to the PREsTo scale, %	15.2 (15.2; 15.2)	5.4 (3.4; 10.0)	0.143
Amsterdam-Oxford PSC Score			
High risk of death according to the Amsterdam-Oxford PSC Score, *n* (%)	2 (66.7)	3 (16.7)	0.140

Note: * — calculation according to the PREsTo score scale was made for one patient who died and five patients who survived during the observation period.

of the disease, is the MELD scale. However, the heterogeneous nature of PSC, slow progression, and variable outcomes limit the predictive value of this index. The use of modern PSC prognostic models is significantly hampered by the fact that existing data are based on different study populations, primary endpoints, and follow-up times. The calculation of indices was carried out two years before the primary end point in the studied sample (the minimum observation period in the deceased group). The MELD score and rMRS index did not show significant differences in patients depending on the outcome. A high risk of death according to the Amsterdam-Oxford PSC Score was in two of the three patients who died, however, in the group of surviving patients, high values were recorded in 16.7 % of cases. The complexity of using the PREsTo score is associated with strict inclusion criteria, which did not allow us to analyze the predictive significance of this index. The UK-PSC Score had the highest predictive value in assessing the risk of death in PSC patients according to the results of our analysis. The result of applying this model showed a high risk in two of the three patients who died and only in one patient in the group of survivors. The advantage of this index is the dynamic assessment of clinical and laboratory parameters: at the time of diagnosis and one year after the start of observation. The data obtained indicate the need for further study of this scale in a larger sample of patients.

Conclusion

The evaluation of the disease prognosis can serve as the basis for the development of patient management algorithms despite the fact that PSC remains a disease with an unfavorable outcome. Current predictive models differ in the parameters used, observation intervals, and endpoints. The UK-PSC Score showed predictive value in patients with a fatal outcome included in the study, which indicates the prospects for further use of this scale for assessing individual risk in real clinical practice.

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Information about the authors

Anastasia I. Dolgushina — Dr. Sci. (Med.), Associate Professor, Head of the Department of Hospital Therapy, South Ural State Medical University.
Contact information: dolgushinaai@yandex.ru;
454092, Chelyabinsk, Vorovskogo str., 64.
ORCID: https://orcid.org/0000-0003-2569-1699

Anna A. Selyanina* — Assistant of the Department of Hospital Therapy, South Ural State Medical University.
Contact information: anna-selyanina@mail.ru;
454092, Chelyabinsk, Vorovskogo str., 64.
ORCID: https://orcid.org/0000-0002-3481-8092

Viktoria V. Dubrovina — 6th year student of the South Ural State Medical University.
Contact information: vikki_1997.97@mail.ru;
454092, Chelyabinsk, Vorovskogo str., 64..
ORCID: https://orcid.org/0000-0002-0824-7214

* Corresponding author / Автор, ответственный за переписку

Сведения об авторах

Долгушина Анастасия Ильинична — доктор медицинских наук, доцент, заведующая кафедрой госпитальной терапии ФГБОУ ВО «Южно-Уральский государственный медицинский университет» Министерства здравоохранения Российской Федерации.
Контактная информация: dolgushinaai@yandex.ru;
454092, г. Челябинск, ул. Воровского, д. 64.
ORCID: https://orcid.org/0000-0003-2569-1699

Селянина Анна Алексеевна* — ассистент кафедры госпитальной терапии ФГБОУ ВО «Южно-Уральский государственный медицинский университет» Министерства здравоохранения Российской Федерации.
Контактная информация: anna-selyanina@mail.ru;
454092, г. Челябинск, ул. Воровского, д. 64.
ORCID: https://orcid.org/0000-0002-3481-8092

Дубровина Виктория Вячеславовна — студентка 6-го курса ФГБОУ ВО «Южно-Уральский государственный медицинский университет» Министерства здравоохранения Российской Федерации.
Контактная информация: vikki_1997.97@mail.ru;
454092, г. Челябинск, ул. Воровского, д. 64.
ORCID: https://orcid.org/0000-0002-0824-7214

Gulnaz A. Isyangildina — 6th year student of the South Ural State Medical University.
Contact information: isangildinagulnaz31@gmail.com;
454092, Chelyabinsk, Vorovskogo str., 64.
ORCID: https://orcid.org/0000-0002-7385-8505

Elena R. Olevskaya — Dr. Sci. (Med.), Associate Professor, Head of the Department of Endoscopy of the Chelyabinsk Regional Clinical Hospital.
Contact information: endo74@mail.ru;
454048, Chelyabinsk, Vorovsky str., 70.
ORCID: https://orcid.org/0000-0002-7385-8505

Исянгильдина Гульназ Амировна — студентка 6-го курса ФГБОУ ВО «Южно-Уральский государственный медицинский университет» Министерства здравоохранения Российской Федерации.
Контактная информация: isangildinagulnaz31@gmail.com;
454092, г. Челябинск, ул. Воровского, д. 64.
ORCID: https://orcid.org/0000-0002-7385-8505

Олевская Елена Рафаиловна — доктор медицинских наук, доцент, заведующая отделением эндоскопии государственного бюджетного учреждения здравоохранения «Челябинская областная клиническая больница».
Контактная информация: endo74@mail.ru;
454048, г. Челябинск, ул. Воровского, д. 70.
ORCID: https://orcid.org/0000-0002-7385-8505

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