Model for predicting of the liver cirrhosis development in children with cystic fibrosis

V.A. Klymenko¹, N.M. Drobova¹, O.V. Piontkovska², O.V. Pasichnyk²

¹Kharkiv National Medical University, Ukraine
²Kharkiv Regional Clinical Children’s Hospital No.1, Ukraine

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Guidelines, liver cirrhosis is a diffuse process dominant in the CF manifestation [1,7]. Signs of lung’s and pancreas’s pathology, which are of liver disease are overshadowed by more obvious clinical signs of death causes in CF patients [8,11]. Despite the fact, that patients with CF are characterized by pathological changes in the liver with the variable severity degrees, liver cirrhosis, as one of the dominant factors of the disease severity is caused by mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) protein with the defeat of the exocrine glands of vital organs and systems [2,6,9].

Liver cirrhosis has been described as a complication of CF in the original description of the pathologist Dorothy Anderson in 1938. However, often the importance of clinical signs of liver disease are overshadowed by more obvious signs of lung’s and pancreas’s pathology, which are dominant in the CF manifestation [1,7].

According to the Evidence-Based Medicine Guidelines, liver cirrhosis is a diffuse process characterized by fibrosis and a transformation of the normal structure of the liver with the formation of nodes. Liver cirrhosis is the final stage of the chronic liver disease and organ damage in CF patients [5,10,13].

The prevalence of liver cirrhosis among patients with CF is 10–30% and among children is 5–10% [3]. Manifestation of liver cirrhosis, as a rule, occurs in the first decade of life, liver cirrhosis is ranked the third in the general list of death causes in CF patients [8,11].

Introduction

Cystic fibrosis (CF) is a genetic disease, which is caused by mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) protein with the defeat of the exocrine glands of vital organs and systems [2,6,9]. Liver cirrhosis has been described as a complication of CF in the original description of the pathologist Dorothy Anderson in 1938. However, often the importance of clinical signs of liver disease are overshadowed by more obvious signs of lung’s and pancreas’s pathology, which are dominant in the CF manifestation [1,7].

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The prevalence of liver cirrhosis among patients with CF is 10–30% and among children is 5–10% [3]. Manifestation of liver cirrhosis, as a rule, occurs in the first decade of life, liver cirrhosis is ranked the third in the general list of death causes in CF patients [8,11].

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It is important to select a cohort of patients with an increased risk of liver cirrhosis development. Prevention of irreversible changes development of the liver parenchyma, relevant correction of the treatment algorithm because of receiving a large number of obligatory medicines, an individual approach to the management of a patient with CF should create the conditions for further improvement of quality and life expectancy of patients with CF.

**Purpose.** To improve medical care for patients with CF by treatment individualization according to the prognosis of the gastrointestinal tract complications development.

**Task.** To create a mathematical model for predicting of the liver cirrhosis development in children with CF.

**Materials and methods**

The research was conducted in the pulmonology department of the Kharkiv Regional Clinical Children’s Hospital No 1 in 2015–2017. Clinical and paraclinical examinations of patient with CF were carried out according to the Order of Ministry of Healthcare of Ukraine of July, 15 2016 No.723 «On approval of the unified clinical protocol of primary, secondary (specialized) and tertiary (highly specialized) medical care «Cystic fibrosis», Order of Ministry of Healthcare of Ukraine of January, 29 2013 No.59 «On approval of unified clinical protocols of medical care for children with diseases of the digestive system».

Patients with CF were divided into 2 groups: group A (with liver cirrhosis) and group B (control, without or with moderate organic liver damage). One hundred twelve indicators were analyzed (passport data (age), complaints, history of disease and life, clinical signs of organs and systems lesions, laboratory and instrumental research results (blood and urine analysis, coprogram, spirometry, electrocardiography, computed tomography of the chest, ultrasound examination of the abdominal cavity, bacteriological examination of sputum, bronchial washings, immunological parameters and total immunoglobulin E (IgE), data of allergy testing, etc.). The logistic regression method with the step-by-step incorporation of predictors was used to analyze the features and to select meaningful criteria for the mathematical model creation. Mathematical processing of the results was carried out using the SPSS 23 package for Windows.

The study was conducted with respect to human rights in accordance with the legislation in force in Ukraine, in compliance with international ethical requirements and didn’t violate ethical norms in science and standards for conducting biomedical research. Informed consent to research was obtained from patients (parents or their caregivers).

**Results**

Forty-two children were examined. Diagnosis of CF was based on clinical and paraclinical characteristics and confirmed by the results of pilocarpine test.

Group A included 9 patients with cirrhotic changes of liver parenchyma and group B (control) comprised 33 patients. There was boys prevalence in the group A (77.8%, p>0.05).

According to age, the majority were children of the senior school age, but there were clinical cases of liver cirrhosis among the toddler children (Table 1).

CF manifestation was represented by the gastrointestinal signs prevalence without a significant difference between the group A and
group B (55.6% and 75.8% respectively, p>0.05). In the majority of group A children, the first signs of the disease were identified during newborn (44.5%) and infant (33.4%) periods.

Regarding the symptoms of the respiratory system, for patients with cirrhotic changes of liver parenchyma there was a tendency for their later manifestation, but with more severe lesions — in the toddler period (66.7%) compared with the control group (in the infant period — 42.3%, p>0.05). The incidences of bronchiectasis (77.8%) and lung fibrosis (100%) were significantly higher (p<0.05) in the group A compared to the group B (30.3% and 69.7% respectively). The evaluation of the bacteriological tests has shown that among the patients in the group A, the following pathogens are significantly more common: *Staphylococcus aureus*, *Enterococcus faecium*, *Candida spp.*, *Enterobacter cloacae*, *Streptococcus mitis*, *Stenotrophomonas maltophilia*.

Table 2

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Group A (n=9)</th>
<th>Group B (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes, $x10^9/l$</td>
<td>5.8 (5.2; 7.05)</td>
<td>6.5 (5.0; 7.7)</td>
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<tr>
<td>Neutrophils, %</td>
<td>47.0 (42.0; 54.0)</td>
<td>49.0 (40.0; 61.0)</td>
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<tr>
<td>Lymphocytes, %</td>
<td>54.0 (46.0; 58.0)*</td>
<td>50.0 (39.5; 61.5)</td>
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<tr>
<td>CD3, %</td>
<td>67.0 (63.0; 71.0)*</td>
<td>61.5 (54.0; 68.0)</td>
</tr>
<tr>
<td>CD4, %</td>
<td>36.0 (33.0; 40.0)*</td>
<td>40.0 (37.0; 45.0)</td>
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<tr>
<td>CD8, %</td>
<td>27.0 (26.5; 28.5)</td>
<td>28.0 (27.0; 29.0)</td>
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<tr>
<td>CD16, %</td>
<td>13.0 (8.5; 15.0)</td>
<td>14.0 (10.0; 16.0)</td>
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<tr>
<td>CD22, %</td>
<td>20.0 (18.0; 20.5)</td>
<td>19.0 (18.0; 20.5)</td>
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<tr>
<td>CD25, %</td>
<td>22.0 (16.5; 37.0)</td>
<td>21.0 (18.5; 37.0)</td>
</tr>
<tr>
<td>Phagocytosis of latex, %</td>
<td>66.0 (56.0; 69.0)</td>
<td>63.0 (58.5; 68.5)</td>
</tr>
<tr>
<td>Phagocytic number</td>
<td>3.8 (3.65; 3.95)</td>
<td>3.8 (3.7; 4.1)</td>
</tr>
<tr>
<td>Total complement (CH 50)</td>
<td>62.0 (59.5; 66.5)</td>
<td>64.0 (61.5; 67.0)</td>
</tr>
<tr>
<td>Circulating immune complexes with 3.5% PEG, units</td>
<td>7.7 (6.35; 9.55)</td>
<td>7.9 (6.8; 9.85)</td>
</tr>
<tr>
<td>Spontaneous nitroblue tetrazolium (NBT) tests, %</td>
<td>26.0 (15.0; 40.0)</td>
<td>25.0 (14.5; 47.0)</td>
</tr>
<tr>
<td>Spontaneous index of activated neutrophils (IAN) test, units</td>
<td>0.34 (0.25; 0.78)</td>
<td>0.39 (0.27; 0.9)</td>
</tr>
<tr>
<td>Stimulated NBT test, %</td>
<td>65.0 (59.0; 70.0)</td>
<td>63.0 (56.0; 71.0)</td>
</tr>
<tr>
<td>Stimulated IAN test, units</td>
<td>1.31 (1.06; 1.49)</td>
<td>1.34 (1.17; 1.49)</td>
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<tr>
<td>Lysosomal cationic proteins, units</td>
<td>1.15 (1.02; 1.21)</td>
<td>1.18 (1.02; 1.25)</td>
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<tr>
<td>IgA, g/l</td>
<td>1.22 (0.83; 1.34)*</td>
<td>1.39 (1.02; 1.56)</td>
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<tr>
<td>IgM, g/l</td>
<td>1.04 (0.83; 1.2)</td>
<td>0.98 (0.83; 1.22)</td>
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<tr>
<td>IgG, g/l</td>
<td>10.18 (9.34; 10.38)*</td>
<td>10.38 (10.23; 10.98)</td>
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<tr>
<td>IgE, $/n$</td>
<td>251.6 (28.1; 556.0)</td>
<td>56.0 (27.1; 183.0)</td>
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* - p<0.05 compared with the group B.

So, observation of patients with CF and liver cirrhosis has revealed a number of clinical and laboratory signs regarding the prognosis of progressive liver damage. Using simple methods of nonparametric statistics during definition of significant conclusions is complicated by the rarity of the pathology and a little number of patients. Therefore, to objectivize the evaluation of the individual factors influence in the liver damage pathogenesis in CF, a logistic regression method was used to determine the coefficients of regression function.

After the mathematical model formation, the binary logistic regression equation, which determines the probability of developing liver cirrhosis in children with CF, has the following form:

$$P = \frac{1}{1 + \exp(-(2.371 x_1 + 0.408 x_2 - 0.810 x_3 + 3.861 x_4 - 3.215 x_5 - 0.558))}$$

where

- $X_1$ — pathology of the gastrointestinal tract (% — no, 2 — yes);
- $X_2$ — CD3 (%);
- $X_3$ — CD4 (%);
- $X_4$ — the presence of bronchiectasis (% — no, 2 — yes);
- $X_5$ — *S. aureus* (in sputum) (% — no, 2 — yes).
The P value is in the range from 0 to 1 and reflects the probability of the risk of developing liver cirrhosis in a child with CF. If P>0.5, it predicts a high risk of liver cirrhosis development, and if P<0.5, it predicts a low risk of liver cirrhosis development.

All variables, according to Wald test, are significant (p<0.05) and are rightly selected. The overall assessment of the agreement between the identified risk factors in the model and the actual observed adverse event was conducted using the Hosmer and Lemeshow test, the accuracy of the classification was 88.1%.

The effectiveness of the proposed mathematical model is illustrated by the following clinical case.

The patient R. was a 13-year-old boy. He was admitted to the Kharkiv Regional Clinical Children’s Hospital No.1 for the preventive treatment course. The patient complained of coughing with periodic sputum of pale yellow color, periodic nausea. The condition was assessed as a moderate due to respiratory and gastrointestinal disorders (Fig.).

It is known, the baby was from the first pregnancy, after 38 weeks of gestation by vaginal delivery with a birth weight of 3100 gm, height of 51 cm.

The baby’s fat stool was identified at the age of 2 months. During the prophylactic examination, the doctor found insufficient weight gain. A cough bothered the child from age of 5 months, and then pneumonia was diagnosed with a severe and protracted course, difficult treatment according to the standard protocols. The child was referred for a medical genetic center, where he was diagnosed with CF based on clinical and paraclinical signs, positive sweat chloride test (142/128 mmol/L) at the age of 10 months. Genetic analysis has found that the child is a carrier of the delF508/N1303K mutation of the CFTR gene. The patient had chronic gastroduodenitis from the age of 3 years old. The patient received treatment in accordance with the national medical standards, but at the age of 3.5 years during the ultrasound examination of the abdominal cavity, cirrhotic changes of the liver parenchyma were identified. On examination: physical growth and development was poor. Body mass index (BMI) was 14.2 kg/m² (equivalent to BMI<10 percentiles). Skin was pale pink, without rash. Deformation of the fingers and fingernails (clubbed fingers and watch-glass nails) were found.

Thoracic cage was the cylindrical shape. Percussion sound was shortened in back basal areas, hyperresonant — in the upper and middle areas. Harsh breathing, moist small- and medium bubbling rales were detected in back basal areas during lung auscultation. Heart sounds were rhythmic, sounding, systolic murmurs in first auscultation point. The abdomen was enlarged due to hepatomegaly (+5.0 cm), splenomegaly (+7.0 cm). Stool was 2–3 times per day. The results of some laboratory studies were as follows: sputum bacteriological tests — *S. aureus* 10⁶, *Streptococcus spp.* 10⁵; the computed tomography of the chest — widespread bilateral cylindrical bronchiectasis; the ultrasound examination of the abdominal cavity — hepatosplenomegaly, expressed diffuse cirrhotic changes in the liver parenchyma (cirrhosis), pancreas parenchyma; immunological research — Leukocytes 5.6x10⁹/L, Neutrophils 49%, Lymphocytes 51%, CD3, 68%, CD4 40%, CD8 38%, CD16 28%, CD22 13%, CD25 18%, Phagocytosis of latex 67%, Phagocytic number 3.5 un., Total complement (CH 50) 69%, CIC with 3.5% PEG 9.9 un., Spontaneous NBT tests 26%, Spontaneous IAN test IAH 0.34 un., Stimulated NBT test 65%, Stimulated IAN test 1.22 un., Lysosomal cationic proteins 1.08 un., IgА 1.22 g/L, IgM 0.85 g/L, IgG 10.28 g/L.


Liver transplantation was recommended according to the severity of liver damage and hepatic insufficiency.

The calculation of the liver cirrhosis risk prognosis by using the mathematical model was done: 

\[
P = \frac{1 + \exp\left(-\left(2.371 \times 2 + 0.408 \times 69 - 0.810 \times 40 + 3.861 \times 2 - 3.215 \times 2 - 0.558\right)\right)}{1} = 0.77.
\]

0.77>0.5 — Conclusion was the high risk of liver cirrhosis. Patient R. has liver cirrhosis corres-
ponding to the prognosis. These data are relevant to prognosis.

The mathematical model is easy to use. Its application should improve the liver cirrhosis risk predicting and timely correction of therapy to prevent the development of this pathology by using standard routine examination methods for patients with CF.

Conclusion

The mathematical model for predicting of the liver cirrhosis development in children with CF was created. It should help to make an individual algorithm for treating using non-specific research methods in order to prevent the progression of liver damage in patients with CF.

The authors declare no conflict of interests.

REFERENCES


