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# Transient elastography, ultrasound imaging and liver enzymes in diagnosis of cystic fibrosis-related liver disease in children

**Abstract.** *Background. Liver disease is responsible for relevant morbidity and mortality in children with cystic fibrosis. We aimed to assess the predictive value of a combination of transient elastography, ultrasound imaging and serum liver enzymes for diagnosis of cystic fibrosis-related liver disease. **Materials and methods.** A total of 108 children aged 0–17 years with cystic fibrosis were examined. The fibrosis stage was determined using transient elastography. The activity of enzymes (alanine transaminase, aspartate transaminase, alkaline phosphatase, gamma-glutamyl transferase, lactate dehydrogenase-5), ultrasound parameters of the liver at different stages of liver fibrosis have been investigated. **Results.** Liver fibrosis of varying severity (F1-F4) was detected in 29.6 % of patients with cystic fibrosis. Liver cirrhosis was observed in 14.8 % of children with cystic fibrosis. The association between an elevated activity of alkaline phosphatase, gamma-glutamyl transferase, lactate dehydrogenase-5, an enlargement of the left lobe of the liver and the degree of fibrosis F1-F4 was found. Moreover, a significant increase in the size of the left lobe corresponded to a higher degree of fibrosis. A reverse correlation was detected between the k coefficient (the ratio of the sizes of the right and left lobes of the liver) and the degree of fibrosis, with a greater degree of fibrosis corresponding to a lower value of this parameter. The maximum enlargement of the left lobe of the liver, the lowest value of the k coefficient, and the dilation of the portal and splenic veins were observed in patients with liver cirrhosis. **Conclusions.** The transient elastography, changing of ultrasound liver parameters with elevated activity of the alkaline phosphatase, gamma-glutamyl transferase, lactate dehydrogenase-5 could be used for early diagnosis of cystic fibrosis-related liver disease.*
**Keywords:** *cystic fibrosis-related liver disease; transient elastography; ultrasound imaging*

## Introduction

Cystic fibrosis (CF) is the most common monogenic autosomal recessive metabolic disorder among people of European descent. It is characterized by a progressive course, disruption of vital functions, early development of complications, premature disability, and a high mortality rate [1]. An increased lifespan of CF patients contributes to the development of severe pathology of hepatobiliary system [2, 3]. Liver disease is responsible for relevant morbidity and mortality in children with CF [2–5]. Literature reports indicate a high frequency of liver involvement in CF (ranging from 20 to 80 %) with a characteristic asymptomatic course [5, 6]. It is known that clinical manifestations of cystic fibrosis-related liver disease (CFLD) occurred in the stage of established cirrhosis, indicating the late diagnosis [4, 7]. There is a suggestion about a correlation between hepatomegaly and the severity of histological changes in the liver, and about the high frequency of CFLD in males; there are differing opinions regarding the association of liver involvement and CF gene mutations [5–8]. From this perspective, it is essential to assess the characteristics of hepatobiliary system involvement in CF and to find the criteria for early diagnosis of CFLD. The need for such research is supported by several authors [1, 8–14].

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**The purpose** of the study was to assess the predictive value of a combination of transient elastography, ultrasound imaging and serum liver enzymes for diagnosis of CFLD.

## Materials and methods

An observational study with collecting of longitudinal data from 108 children with CF attending the Cystic Fibrosis Center within the Regional Children's Clinical Hospital (Odesa, Ukraine) between 2010 and 2020 was performed. Inclusion criteria for the study were: CF diagnosis; age 0 to 17 years; absence of other chronic comorbidities; informed consent from both parents and the child for participation in the research. Exclusion criteria were as follows: severe congenital or acquired comorbidities; lack of consent from parents and/or the child for participation in the study.

**Patient involvement.** Patients and their families (parents or caregivers) were involved in the planning and conducting a survey. They were intimately involved in the setting of priority issues, defining research questions, outcome measures, and design. Patient partners (parents or caregivers) promoted the study to the target audience and played the key role in the recruitment effort. They were central to dissemination of the baseline information about the survey, which helped motivate patients and community during and beyond the study. Finally, they reviewed and confirmed the results and conclusions.

Patients attended the CF center at least once a year where they had a traditional clinical examination. All patients had genetic testing for the disease regarding CFTR mutation.

The hepatic status was evaluated in all patients, including biochemical measurements (alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and lactate dehydrogenase-5 (LDH-5)), abdominal ultrasonography and transient elastography on the FibroScan® 502 (Echosens, Paris, France). Elastography allowed for a quantitative assessment of liver stiffness in kilopascals (kPa) and determination of the fibrosis stage according to the METAVIR scale: liver stiffness ≤ 5.8 kPa corresponded to absence of fibrosis (F0), 5.9–7.0 kPa — F1 fibrosis, 7.1–9.4 kPa — F2 fibrosis, 9.5–12.5 kPa — F3 fibrosis, > 12.5 kPa — F4 fibrosis, or liver cirrhosis [15, 16]. Liver biopsy was not performed due to its invasiveness and the high risk of complications. The diagnosis of CFLD relied on classical criteria: if two or more categories were present including abnormal liver function tests (increase of ALT, AST, GGT above upper limits in at least three consecutive determinations over 12 months after excluding other causes), abnormal physical examination (hepatomegaly, splenomegaly confirmed by ultrasonography), ultrasonographic evidence of liver involvement or portal hypertension, or biliary abnormalities [8].

Statistical data analysis was conducted using the software package Statistica 10 (StatSoft Inc., USA) and the online calculator SISA (Simple Interactive Statistical Analysis). To test statistical hypotheses regarding differences in relative frequencies in independent samples, odds ratios and the achieved level of significance (p) were calculated. Differences were considered non-random when the probability was $p < 0.05$. The biases from ignoring the frequency-matched design in the analysis are relatively small and similar in magnitude to those seen on conditional analyses. A conditional logistic regression sensitivity analysis was performed using the frequency-matched sets.

## Results

From 2010 to 2020, 108 children aged 0−17 with CF were examined. General clinical examination revealed hepatomegaly, with the liver enlarged by 1 to 5 cm below the costal margin in 98 patients (90.7 %). In 32 cases (29.6 %), the liver was firm in consistency and painless, while in 10 (9.3 %), it had an uneven, nodular surface. Enlargement of the spleen from 1 to 7 cm was observed in 8 children (7.4 %). On ultrasound examination, most patients (88.9 %) exhibited heterogeneous acoustic structure of the liver. Clinical manifestations of CFLD were characterized by a mild and latent course, and the results of routine hematological and biochemical studies were not informative for specifying pathological changes in the liver parenchyma. Diagnosis of structural abnormalities was only possible through modern visualization methods. The distribution of CF children by the severity of liver fibrosis according to transient elastography

*Table 1 — Epidemiological characteristics of patients with CFLD, fibrosis F1–3, cirrhosis F4 and without CFLD in a cohort of children with CF*

| | Total (n = 108) | No CFLD (n = 76) | CFLD, F1–3 (n = 16) | CFLD, F4 (n = 16) |
|---|---|---|---|---|
| **Sex** | | | | |
| Male | 58 (53.7) | 34 (44.7) | 10 (62.5)* | 14 (87.5)** |
| Female | 50 (46.3) | 42 (55.3) | 6 (37.5) | 2 (12.5) |
| **Age group, years** | | | | |
| 0–3 | 20 (18.5) | 18 (23.7) | 2 (12.5) | 0 (0.0) |
| 4–6 | 34 (31.5) | 24 (31.6) | 6 (37.5) | 4 (25.0) |
| 7–9 | 30 (27.8) | 20 (26.3) | 4 (25.0) | 6 (37.5) |
| 10–17 | 24 (22.2) | 14 (18.4) | 4 (25.0) | 6 (37.5) |
| **ΔF508 mutation in genotype** | | | | |
| Homozygote ΔF508 | 60 (55.6) | 34 (44.7) | 11 (68.8)* | 15 (93.8)** |
| Heterozygote ΔF508 | 34 (31.5) | 30 (39.5) | 4 (25.0) | 0 (0.0) |
| Other CFTR mutation | 14 (12.9) | 12 (15.8) | 1 (6.2) | 1 (6.2) |

*Notes: here and in the Table 2: data are presented as n (%); \* — significant difference between patients without CFLD and with CFLD, fibrosis F1–3 (p < 0.05), \*\* — significant difference between patients with CFLD, fibrosis F1–3, and with CFLD, cirrhosis F4 (p < 0.05).*

(FibroScan, Echosens, France) was as follows: F0 (absence of fibrosis) — 76 patients (70.4 %), F1 (minimal fibrosis) — 3 children (2.8 %), F2 (moderate fibrosis) — 5 children (4.6 %), F3 (severe fibrosis) — 8 children (7.4 %), F4 (liver cirrhosis) — 16 patients (14.8 %).

We compare three groups of patients: without CFLD, with CFLD, fibrosis F1–3, and with CFLD, cirrhosis F4. The comparison of epidemiological characteristics of patients are shown in the Table 1.

No difference in age ($p \geq 0.05$) was shown between patients with and without CFLD. However, there were significant differences in sex category and CFTR mutations (homozygote ΔF508) between CFLD and non-CFLD patients.

When categorizing CF patients by age, a trend to CFLD worsening with increasing life expectancy was observed. Among children aged 0 to 3 years, CFLD was noted in 10 % (95% confidence interval (CI) 3.14–23.14 %), 4 to 6 years — in 29.41 % (95% CI 13.74–44.25 %), 7 to 9 years in 33.33 % (95% CI 16.17–49.82 %), and among those aged 10 to 17 years — in 41.67 % (95% CI 22.25–61.74 %). Given the progressive natural history of liver fibrosis, age is an important risk factor for CFLD.

A significant predominance of males among CF patients with CFLD was found: fibrosis (F1-F4) was detected in 41.38 % of boys (95% CI 29.29–54.70 %) and 16 % of girls (95% CI 5.10–24.89 %). The odds ratio for developing CFLD in males compared to females was 3.7 (95% CI 1.47–9.29), and the relative risk of fibrosis F1-F4 was 2.59 (95% CI 1.24–5.85). Male gender in CF patients should be considered an adverse prognostic factor for the CFLD.

The analysis of CF patient genotypes revealed that among homozygotes for the ΔF508 deletion, the frequency of CFLD was 43.33 % (95% CI 30.47–55.52 %), among heterozygotes with the ΔF508 deletion together with other mutations — 11.76 % (95% CI 1.07–22.92 %), and among patients with mutations other than ΔF508 — 14.28 % (95% CI 4.17–32.17 %). The odds ratio for CFLD in patients with the ΔF508 deletion in their genotype was 2.81 (95% CI 0.59–13.36), and the relative risk was 2.23 (95% CI 0.67–13.25).

The assessment of the prognostic value of the studied medical-biological factors regarding the development of CFLD revealed high sensitivity, moderate specificity, and positive prognostic value for the following parameters: age of the CF patient over 7 years (0.63, 0.55, and 0.37, respectively), and male gender (0.75, 0.55, and 0.41, respectively). It is recommended to use the proposed criteria for identifying high-risk group for the CFLD.

The ultrasound liver parameters and liver enzymes activity (ALT, AST, ALP, GGT, and LDH-5) were assessed in patients without CFLD, with CFLD, fibrosis F1–3, and with CFLD, cirrhosis F4. The comparison of ultrasound and laboratory characteristics of patients with and without CFLD are shown in the Table 2.

We observed that the progression of fibrosis was associated with an enlargement of the left lobe of the liver. Moreover, a significant enlargement of the left lobe corresponded to a higher degree of fibrosis (F1–3 and F4) ($p < 0.05$). An inverse relationship was found between the k coefficient (the ratio of the sizes of the right and left lobes of the liver) and the degree of fibrosis ($p < 0.05$). The maximum enlargement of the left lobe of the liver, the lowest value of the k coefficient, and the dilation of the portal and splenic veins were detected in patients with liver cirrhosis (F4). The obtained data support the rationale for using ultrasound liver parameters for early diagnosis of CFLD.

Assessing the proposed criteria for early diagnosis of CFLD revealed that the ultrasound parameters of the liver had the highest positive prognostic value, namely the enlargement of the left liver lobe (0.75), the k coefficient of the right-to-left liver lobes (0.80), and the dilation of the portal and splenic veins (0.88).

The ALT and AST activity remained within normal ranges in CF patients with fibrosis stages F0-F3 but significantly increased in those with cirrhosis F4 ($p < 0.05$). Therefore, routine biochemical tests were not able to detect CFLD at early stages.

We observed that the progression of CFLD was associated with an elevated activity of ALP, GGT, and LDH-5, with the highest activity in cirrhosis ($p < 0.001$). It also confirmed the high sensitivity (0.94) and moderate positive prognostic value of the elevated activity of ALP, GGT, and LDH-5 for diagnosis of CFLD. The obtained data support the rationale for using the elevation of ALP, GGT, and LDH-5 activity for early diagnosis of CFLD.

*Table 2 — Ultrasound liver parameters and liver enzyme activity in patients with CFLD, fibrosis F1–3, cirrhosis F4 and without CFLD in a cohort of children with CF*

| Characteristics | No CFLD (n = 76) | CFLD, F1–3 (n = 16) | CFLD, F4 (n = 16) |
|---|---|---|---|
| **Ultrasound liver parameters (upper normal limit)** | | | |
| Enlargement of the right lobe of the liver, mm | 0.40 ± 0.03 | 4.80 ± 1.10* | 0.20 ± 0.02 |
| Enlargement of the left lobe of the liver, mm | 0.40 ± 0.02 | 19.4 ± 1.1* | 31.5 ± 1.4** |
| Coefficient k of the liver lobes ratio | 1.60 ± 0.10 | 1.30 ± 0.08* | 1.00 ± 0.30** |
| Portal vein dilation, mm | 0.0 ± 0.0 | 0.0 ± 0.0 | 2.5 ± 0.5** |
| Splenic vein dilation, mm | 0.0 ± 0.0 | 0.0 ± 0.0 | 1.9 ± 0.3** |
| **Liver enzyme activity** | | | |
| ALT, IU/L | 23.5 ± 1.3 | 28.7 ± 4.7 | 72.4 ± 14.8** |
| AST, IU/L | 18.7 ± 2.1 | 29.5 ± 2.4 | 69.6 ± 2.8** |
| ALP, IU/L | 320.3 ± 9.3 | 455.8 ± 39.3* | 628.1 ± 47.5** |
| GGT, IU/L | 28.6 ± 3.1 | 54.3 ± 8.1* | 128.3 ± 21.2** |
| LDH-5, % | 7.6 ± 0.4 | 23.0 ± 1.8* | 32.3 ± 4.3** |

## Discussion

The use of advanced medical technologies, aggressive therapeutic regimens, and transplantation programs in CF patients has become an objective factor contributing to an increase in the frequency of late complications of the disease. CFLD is the second leading cause of death after lung complications [1−4].

In-depth research into the features of CFLD was conducted in 108 children with CF. Clinical manifestations of biliary pathology differed with a mild and latent course, and the results of routine biochemical tests were not informative for detecting pathological changes in the liver parenchyma. Diagnosis of structural abnormalities required modern imaging methods with the detection of fibrosis severity using the METAVIR scale.

The conducted transient elastography of the liver (Fibro-Scan, Echosens, France) showed the absence of fibrosis in 70.4 % of CF patients and the presence of fibrotic changes of varying severity in 29.6 % (with a range of liver elasticity median values from 5.9 to 49.0 kPa), with half of them (14.8 %) having liver cirrhosis. The results indicate a high frequency (in every third patient) of CFLD, which can lead to a fatal outcome and is consistent with previous research findings [1, 3−6, 19−21].

The trend of progressive CFLD with increasing patient lifespan has been established: liver involvement was observed in 10 % of children aged 0−3 years, 29.41 % aged 4−6 years, 33.33 % aged 7−9 years, and in 41.67 % of those aged 10−17 years. These findings confirm the association between the severity of CFLD and disease duration. These results align with existing literature data on the increasing frequency and severity of hepatobiliary system involvement in CF with prolonged patient survival [1, 5−8, 17−19].

The study revealed a significant predominance of males among patients with CFLD: fibrosis (F1-F4) was observed in 41.38 % of boys and 16 % of girls. Therefore, CFLD occurs much more frequently in boys than in girls. The odds ratio of developing CFLD in males compared to females was 3.7 (95% CI 1.47−9.29), and the relative risk of CFLD was 2.59 (95% CI 1.24−5.85). Male gender in CF patients is considered an unfavorable prognostic factor for the development of CFLD. These results are consistent with findings from some authors, indicating a high frequency of hepatobiliary system involvement in males and the predominance of cirrhosis formation in boys [1, 3, 5, 21].

The study confirmed a high frequency of CFLD among homozygotes for the ΔF508 deletion (43.33 %) compared to heterozygotes with the ΔF508 deletion together with other mutations (11.76 %) and among patients with mutations other than ΔF508. The odds ratio for developing CFLD in CF patients with the ΔF508 deletion was 2.81 (95% CI 0.59−13.36), and the relative risk was 2.23 (95% CI 0.67−13.25). It is known that among the studied mutations of the CF gene, there is no specific mutation that directly causes liver involvement [5, 6, 10, 14, 21].

The progression of CFLD was accompanied by an elevated activity of serum enzymes, including ALP, GGT, and LDH-5. The direct correlation was revealed between the elevated activity of ALP, GGT, and LDH-5 and the degree of fibrosis from F1 to F4 (p < 0.05). These findings are consistent with the results of previous scientific studies [11−13, 16−21].

The progression of CFLD was associated with an enlargement of the left lobe of the liver and decreasing coefficient k (the ratio of the sizes of the right and left lobes of the liver). The correlation was found between these deviations and the degree of fibrosis from F1 to F4 (p < 0.05), which is in line with reports from some researchers [17−21].

## Conclusions

The combined use of transient elastography (FibroScan) with elevated activity of the ALP, GGT, and LDH-5 enzymes and changing of ultrasound liver parameters (enlargement of the left lobe of the liver, a reduction in the k ratio of the sizes of the right and left lobes of the liver, dilatation of the portal and splenic veins) could be used for early diagnosis of CFLD. The age of a patient with CF over 7 years, male gender and the presence of ΔF508 deletion in the genotype have a high positive predictive value for CFLD with liver fibrosis and cirrhosis.

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### Транзієнтна еластографія, ультразвукова візуалізація та печінкові ферменти в діагностиці хвороби печінки при муковісцидозі в дітей

**Резюме.** *Актуальність.* Хвороба печінки є причиною значної захворюваності та смертності дітей із муковісцидозом. *Метою дослідження* була оцінка прогностичної цінності транзієнтної еластографії, ультразвукової візуалізації і печінкових ферментів щодо діагностики хвороби печінки при муковісцидозі. *Матеріали та методи.* Обстежено 108 дітей віком 0—17 років, хворих на муковісцидоз. Стадію фіброзу визначали за допомогою транзієнтної еластографії. Досліджували активність ферментів (аланінамінотрансфераза, аспартатмінотрансфераза, лужна фосфатаза, гамма-глутамілтрансфераза, лактатдегідрогеназа-5), ультразвукові параметри печінки на різних стадіях фіброзу. *Результати.* У 29,6 % хворих на муковісцидоз встановлено фіброз печінки різного ступеня вираженості (F1-F4), у 14,8 % діагностовано цироз печінки. Виявлений зв'язок між підвищенням активності лужної фосфатази, гамма-глутамілтрансферази, лактатдегідрогенази-5, збільшенням лівої частки печінки та ступенем фіброзу F1-F4. Крім того, значне збільшення розмірів лівої частки відповідало вищому ступеню фіброзу. Виявлено зворотну кореляцію між коефіцієнтом k (співвідношення розмірів правої та лівої часток печінки) і ступенем фіброзу, причому вищому ступеню фіброзу відповідало менше значення цього параметра. У хворих на цироз печінки спостерігалося максимальне збільшення лівої частки печінки, найменше значення коефіцієнта k, розширення діаметрів ворітної та селезінкової вен. *Висновки.* Транзієнтна еластографія, зміни ультразвукових параметрів печінки разом із підвищеною активністю лужної фосфатази, гамма-глутамілтрансферази, лактатдегідрогенази-5 можуть бути використані для ранньої діагностики хвороби печінки при муковісцидозі.

**Ключові слова:** муковісцидоз; хвороба печінки; транзієнтна еластографія; ультразвукова візуалізація