Genetic and clinical factors influencing CF-associated liver disease: the impact of *SERPINA1* variants and *CFTR* genotypes in Romanian pediatric cystic fibrosis patients

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Abstract

Background. Hepatic disease represents a significant complication in children with cystic fibrosis (CF), yet its relationship with specific genetic factors, including CFTR (Cystic fibrosis transmembrane conductance regulator) mutations and SERPINA1 alleles, is not well understood. This study aims to clarify these associations within a Romanian pediatric CF population.

Methods. In this cross-sectional, prospective study, we examined 71 children with CF, comparing those with hepatic disease (n=25) to those without (n=46). We collected comprehensive clinical, biochemical, and genetic data, focusing on CFTR genotypes and SERPINA1 alleles. Key outcomes included the prevalence of hepatic disease in relation to specific genotypes, fibrosis markers, and liver function tests.

Results. The DF508/DF508 genotype was the most prevalent, occurring in 49% of the cohort. No significant associations were found between hepatic disease and specific CFTR genotypes or SERPINA1 alleles. However, children with hepatic disease exhibited significantly higher fibrosis scores (APRI and FIB-4), suggesting more advanced liver involvement. Additionally, a slight delay in CF diagnosis was observed in those with hepatic disease, though this difference did not reach statistical significance.

Conclusion. This pioneering study in Romania underscores the complexity of hepatic disease in CF. While specific CFTR genotypes and SERPINA1 alleles were not significantly associated with hepatic complications, the findings emphasize the importance of early diagnosis and monitoring using fibrosis markers to identify children at risk for liver involvement.

Keywords: cystic fibrosis, hepatic disease, CFTR genotypes, SERPINA1 alleles

Introduction

Cystic fibrosis (CF) is a genetic disorder primarily affecting the respiratory and digestive systems, caused by mutations in the CFTR (Cystic fibrosis transmembrane conductance regulator) gene. Globally, CF affects approximately 70,000 to 100,000 individuals, with prevalence rates varying significantly across regions. In Europe, the incidence ranges from 1 in 2,000 to 1 in 3,500 live births, while in the United States, it is about 1 in 3,500 live births [1,2]. Similar prevalence rates are observed in other parts of the world, including Australia and Canada. CF is typically diagnosed in infancy or early childhood. Thanks to advancements in treatment, life expectancy has improved significantly, with many patients now living into their 40's and beyond [3]. Despite these improvements, CF continues to impose a substantial disease burden, characterized by frequent hospitalizations, intensive treatments, and significant healthcare costs [4].

The importance of studying CF, particularly in children, lies in its significant morbidity and mortality. Complications related to CF, such as lung infections and pancreatic insufficiency, contribute heavily to this burden. Furthermore, CF-associated liver disease (CFLD) is emerging as a notable cause of morbidity and mortality, affecting approximately 23% of CF patients [5]. CFLD can manifest as hepatic steatosis, fibrosis, and cirrhosis, and it is the third leading cause of death in CF patients [6]. Understanding the genetic and clinical factors associated with CFLD is crucial for improving patient outcomes and developing targeted therapies.

CFLD is a significant complication in CF, with prevalence increasing with age. The pathophysiology of CFLD is complex and multifactorial, involving both genetic predispositions, such as mutations in the *CFTR* gene, and environmental factors [7]. Hepatic steatosis is one of the most common forms of CFLD, affecting 15% to 60% of CF patients [8]. The presence of liver disease in CF patients is associated with increased morbidity, including the risk of liver transplantation in severe cases [5]. Therefore, identifying patients at risk for CFLD and understanding the underlying mechanisms are essential for early intervention and management.

The *SERPINA1* gene encodes alpha-1 antitrypsin, a protein that protects tissues from enzyme damage. Variants in this gene, specifically the S and Z alleles, have been associated with liver disease. The Z allele, in particular, is a well-known risk factor due to its role in protein misfolding and accumulation in the liver [9]. In the context of CF, the presence of the *SERPINA1* Z allele has been linked to an increased risk of developing CFLD [10]. Understanding the role of these genetic variants in CF patients can provide insights into the pathogenesis of liver disease and suggest potential therapeutic targets.

Several studies have explored the association between the *SERPINA1* alleles and CFLD in CF patients. Research indicates that the presence of the *SERPINA1* Z allele is significantly associated with an increased risk of CFLD [8,11]. Comparative studies have shown that CF patients with the Z allele are more likely to develop liver disease compared to those without this genetic variant [10]. Additionally, the S allele, although less studied, may also contribute to liver disease risk in CF patients [9]. These findings underscore the importance of genetic screening in CF patients to identify those at higher risk for liver complications.

This study aims to compare children with CF who have hepatic disease to those without hepatic disease, focusing on the presence of *SERPINA1* S and *SERPINA1* Z alleles, as well as other clinical characteristics. By identifying genetic and clinical differences between these two groups, the study seeks to enhance the understanding of CFLD pathogenesis in CF and inform strategies for early diagnosis and targeted interventions.

Methods

Study design and setting

This cross-sectional observational study included 71 children with CF who were recruited from two hospitals in Bucharest between November 2023 and March 2024. Patients were enrolled in the order of their arrival for follow-up visits, respiratory exacerbations, or other health issues. The participants were selected from the Regional Reference Center for Cystic Fibrosis at the National Institute for Mother and Child Health "Alessandrescu-Rusescu" and the "Grigore Alexandrescu" Emergency Clinical Hospital for Children.

Participants

Inclusion and exclusion criteria

Inclusion criteria: All patients under 18 years of age with a confirmed diagnosis of CF, regardless of the presence or absence of CF-related liver disease.

Exclusion criteria: Patients with an uncertain CF diagnosis, either due to inconclusive sweat test results—the "gold standard" for diagnosis or the absence of a confirmatory genetic test in cases where the diagnosis was not definitive.

Withdrawal criteria: Participants were allowed to withdraw from the study at any time prior to the final data analysis without any consequences.

Children aged 0 to 18 years with a confirmed diagnosis of CF were eligible for inclusion in the study. The diagnosis was established based on clinical criteria and confirmed through either sweat chloride testing or genetic testing. Participants were categorized into two groups: those with hepatic disease and those without. Hepatic disease was defined by the presence of clinical, laboratory, or ultrasound evidence of liver involvement.

Patients with chronic liver diseases unrelated to CF or those who had undergone liver transplantation were excluded from the study. The two groups were defined as follows:

• ***Case group:*** Children with known liver involvement, classified according to the latest guidelines from the CF Foundation [12]. This group included patients with CF hepatic biliary involvement (CFHBI) and advanced CF liver disease (aCFLD)[12].

• ***Control group:*** Children with CF (PwCF) who had no known liver involvement at the time of inclusion [12].

This classification ensured that the case group included all patients with significant liver involvement, while the control group consisted of children with CF without any documented liver disease.

Recruitment and consent

Participants were recruited consecutively from the CF clinic. Written informed consent was obtained from the parents or legal guardians of all participants, while assent was obtained from children aged 12 years and older.

Data collection encompassed a broad range of variables to thoroughly characterize the demographic and clinical profiles of the participants.

• Demographic Data: Information gathered included age at the time of the study (recorded in years) and sex. Age at CF diagnosis was documented in months.

• Clinical History: The clinical history of participants was assessed for the presence of meconium ileus, pancreatic insufficiency, and CF-related diabetes.

• Anthropometric Measurements: These included weight (in kilograms) and height (in centimeters).

• Hepatic Disease Indicators: Hepatic involvement was assessed through clinical examination and imaging studies. Key indicators included hepatosplenomegaly, biliary lithiasis, hepatic changes on ultrasound, cirrhosis, periportal fibrosis, and hepatomegaly. Hepatic and biliary involvement were further categorized into aCFLD, CFHBI, and PwCF. Clinical assessments also recorded the presence of hepatomegaly and splenomegaly, as well as ultrasound-diagnosed liver disease.

• Biochemical Markers: Key biochemical markers included aspartate aminotransferase (AST), alanine aminotransferase (ALT), the AST/ALT ratio, and gamma-glutamyl transferase (GGT), all measured in units per liter. Liver function and fibrosis were evaluated using the GPR Score, APRI Score, and FIB-4 Score. These scores were calculated using the following formulas:

○ GPR Score = [(GGT/ULN GGT)/PLT] × 100, where ULN is upper limit of normal

○ APRI Score = [(AST/ULN AST)/PLT] × 100

○ FIB-4 Score = [(Age * AST) / (Platelets x √(ALT))]

• Treatment: the use of ursodeoxycholic acid (UDCA) and CFTR modulators as treatment options was documented.

• Genetic data: genetic analysis focused on the participants' CFTR genotype, categorized into homozygous DF508/DF508, heterozygous DF508/Others, and Others/Others. Genotypes were further classified based on disease severity. The presence of SERPINA1 S and SERPINA1 Z alleles was also examined, specifically comparing C/T versus C/C genotypes for SERPINA1 Z and A/T versus T/T genotypes for SERPINA1 S.

Data sources and measurement

Data were from multiple sources, including patient medical records, clinical examinations, laboratory test results, and genetic testing reports. The genotyping of SERPINA1 variants was conducted specifically for this study. Hepatic involvement was assessed through clinical evaluations, ultrasound imaging, and liver function tests. Genetic data for *CFTR* mutations, were obtained from previously conducted genetic tests documented in the patients' medical records.

DNA extraction and genotyping

In our study we perform genotyping SERPINA1 alelles for all 71 patients.

The genotyping was performed in the Department of Cell and Molecular Biology at the Iuliu Haţieganu University of Medicine and Pharmacy from Cluj-Napoca, Romania. Genomic DNA samples were isolated using a Kurabo QuickGene-Mini80 Nucleic Acid Isolation System with the QuickGene DNA kit (Kurabo, Osaka, Japan) from peripheral whole blood samples collected on EDTA, and stored at -20^0C until analysis.

SERPINA1 rs28929474 (Pi*Z) SNP and SERPINA1 rs17580 (Pi*S) SNP were genotyped by real-time PCR (RT-PCR), using TaqMan® allelic discrimination assays with TaqPath ProAmp Master Mix (Thermo Fisher Scientific) and CFX Real-Time PCR System (Bio-Rad Laboratories Inc).

Ethical statement

Ethical approval was granted by Institutional Review Board - IRB of the "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca (AVZ 71/ 19.04.2024), in accordance with the Helsinki Declaration guidelines.

Statistical analysis

Qualitative data were reported as frequencies and percentages, while non-normally distributed continuous data were summarized using medians and interquartile ranges. Associations between categorical variables were assessed using the chi-squared test. For cells with expected counts less than five, Fisher's exact test was used to ensure accuracy. To compare two independent groups on non-normally distributed continuous variables, the Mann-Whitney U test was applied. Cumulative incidence plots were generated to compare age at diagnosis, and survival curves were compared using the log-rank test. All statistical tests were two-sided, with a significance threshold set at $p < 0.05$. Statistical analyses were performed using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) [13].

Results

A total of 71 participants were enrolled in the study. The median age of the participants was 9 years (interquartile range: 5 to 13), with ages ranging from 0 to 17 years. Comprehensive patient evaluations are detailed in table I. The analysis revealed that children with CF who developed hepatic disease were generally older and exhibited a higher prevalence of specific hepatic complications, such as biliary lithiasis, periportal fibrosis, and hepatomegaly, compared to those without hepatic disease. Additionally, these children had higher scores on fibrosis markers (APRI and FIB-4), indicating more advanced liver involvement. The observed difference in the use of UDCA between the two groups underscores the tailored clinical management approach for hepatic disease in this population.

The genetic results were independently interpreted by two researchers, both of whom arrived at the same conclusions:

- **For SERPINA1 rs28929474 (Pi*Z) SNP** out of seventy-one patients, seventy are homozygous for C/C genotype, one is heterozygous for C/T genotype.
- **For SERPINA1 rs17580 (Pi*S) SNP** out of seventy-one patients, sixty-nine are homozygous for T/T genotype, two are heterozygous for A/T genotype.

Table I. Comprehensive patient evaluations.

Liver disease	Yes (n=25)	No (n=46)	P-value
Age at the time of the study (years), median (IQR)	11 (8 - 14)	7.5 (4.25 - 13)	0.093
Sex (F), n (%)	15 (60)	21 (45.65)	0.248
Age at diagnosis (months), median (IQR)	3.5 (1 - 22.5)	3 (1 - 10.5)	0.441
History of meconium ileus, n (%)	4 (16.67)	6 (13.04)	0.727
History of pancreatic insufficiency, n (%)	24 (100)	45 (97.83)	1
History of CF-related diabetes, n (%)	1 (4.17)	3 (6.52)	1
Weight (kg), median (IQR)	32.8 (24 - 49)	21.75 (13.25 - 41.75)	0.06
Height (cm), median (IQR)	141 (125 - 158)	127.5 (100.25 - 154)	0.175
Segmental hepatosplenomegaly, n (%)	1 (4)	0 (0)	0.352
Biliary lithiasis, n (%)	4 (16)	0 (0)	0.013
Ultrasound-detected hepatic changes, n (%)	11 (44)	0 (0)	< 0.001
Cirrhosis, n (%)	2 (8)	0 (0)	0.121
Periportal fibrosis, n (%)	3 (12)	0 (0)	0.04
Hepatomegaly, n (%)	4 (16)	0 (0)	0.013
Hepatic and biliary involvement, n (%)			< 0.001
aCFLD	2 (8)	0 (0)	
CFHBI	23 (92)	0 (0)	
PwCF	0 (0)	46 (100)	
Clinical hepatomegaly, n (%)	2 (8)	0 (0)	0.128
Clinical splenomegaly, n (%)	0 (0)	0 (0)	1
Ultrasound diagnosis of liver disease, n (%)	25 (100)	0 (0)	< 0.001
AST in UI, median (IQR)	36 (29 - 47)	29.5 (25 - 41.75)	0.137
ALT in UI, median (IQR)	37 (21 - 59)	30 (24 - 44.5)	0.496
AST/ALT ratio, median (IQR)	1 (0.71 - 1.39)	1.04 (0.81 - 1.31)	0.857
GGT in UI, median (IQR)	22 (15 - 37)	20 (17 - 26.75)	0.206
GPR Score = [(GGT/ULN GGT)/PLT] × 100, median (IQR)	0.22 (0.1 - 0.39)	0.14 (0.11 - 0.21)	0.169
APRI Score = [(AST/ULN AST)/PLT] × 100, median (IQR)	0.27 (0.22 - 0.49)	0.22 (0.17 - 0.29)	0.006
FIB-4 Score = (Age* x AST) / (Platelets x √(ALT)), median (IQR)	0.2 (0.13 - 0.34)	0.14 (0.06 - 0.18)	0.014
On UDCA treatment, n (%)	18 (72)	4 (8.7)	< 0.001
On CFTR modulators treatment, n (%)	14 (56)	26 (56.52)	0.966

IQR, interquartile range; aCFLD, advanced CF liver disease; CFHBI, CF hepatic biliary involvement; PwCF, Children with CF; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; GGT, Gamma-glutamyl transferase; ULN, upper limit of normal; UDCA, ursodeoxycholic acid; CFTR, cystic fibrosis transmembrane conductance regulator.

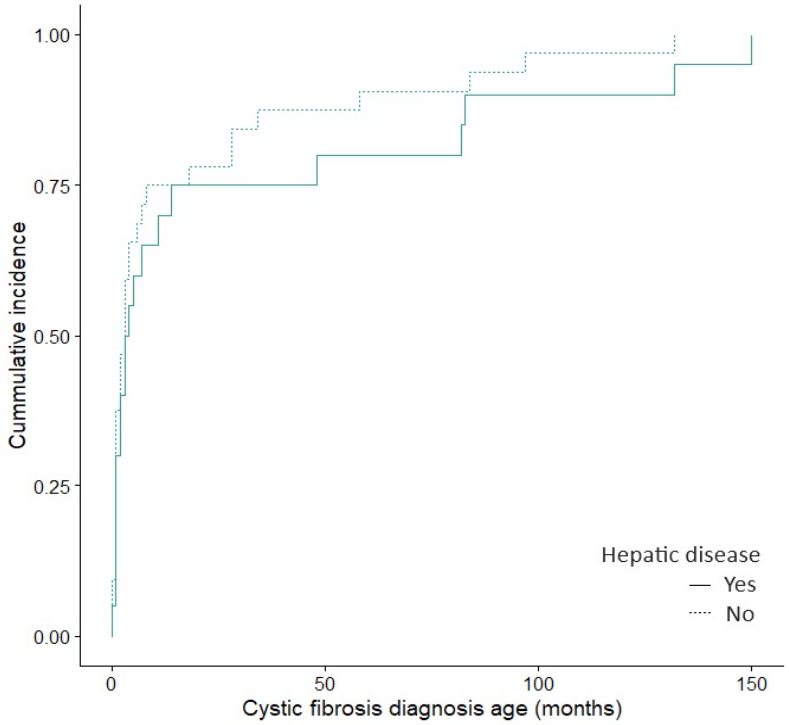

Figure 1. Cumulative incidence of cystic fibrosis diagnosis by age, stratified by hepatic disease status.

Table II. Genotypes in relation with hepatic disease.

Liver disease	Yes (n=25)	No (n=46)	P-value
Genotype, nr (%)			0.51
DF508/DF508	10 (40)	25 (54.35)	
DF508/Others	9 (36)	13 (28.26)	
Others/Others	6 (24)	8 (17.39)	
Genotype according to disease severity (Severe), n (%)	18 (75)	31 (75.61)	0.956
SERPINA1 Z (C/T vs C/C), nr (%)	0 (0)	1 (2.17)	1
SERPINA1 S (A/T vs T/T), nr (%)	1 (4)	1 (2.17)	1

We compared the cumulative incidence of CF diagnosis based on the presence of hepatic disease (Figure 1). Both groups exhibited a rapid increase in cumulative incidence at a very early age, indicating that most children with CF are diagnosed within the first few months of life, irrespective of whether they develop hepatic disease. However, the group with hepatic disease showed a slightly lower cumulative incidence compared to the group without hepatic disease, suggesting that children who develop hepatic disease are diagnosed with CF marginally later. Despite this observation, the difference was not statistically significant ($p = 0.300$). By approximately 50 months of age (about 4 years), the cumulative incidence of CF diagnosis approached 100% in both groups, indicating that nearly all children in both cohorts are diagnosed by this age.

Genotype analysis

No significant differences were observed in genotypes between patients with hepatic disease and those without (Table II). The DF508/DF508 genotype was slightly more prevalent among patients without hepatic disease, while the DF508/Others and Others/Others genotypes were more common in those with hepatic disease. The severity of the disease was comparable between the two groups.

For *SERPINA1* Z, there was only one patient with the C/T genotype in the group without hepatic disease; all other patients in this group had the C/C genotype. For *SERPINA1*

S, one patient in each group had the A/T genotype, while all other patients had the T/T genotype.

A detailed description of the genotypes is provided in table III. The analysis revealed several combinations of CFTR mutations among the patients, highlighting the genetic diversity characteristic of CF. The most common genotype observed was DF508/DF508, present in 35 patients, which aligns with global trends where the DF508 mutation is the most prevalent CFTR mutation.

Table III. Detailed description of genotypes.

Genotypes	Number of patients	Phenotype	Total
CFTR dele 2,3 /G542X	1	SEVERE	49
DF508/R553X	3		
DF508/CFTRdele2,3	1		
DF508/DF508	35		
DF508/E822X	1		
DF508/G542X	3		
DF508/R1066C	1		
DF508/R1066H	1		
DF508/R1158X	2		
G85E/S549N	1		
L227R/W1282X	1	UNCLASSIFIED	22
DF508/1677delTA,7T,9T	1		
DF508/R347P	1		
DF508/C3717 G>A	1		
c.828>Ap.Cys276*/c.2052delAp.Lys684Asnfs*38	1		
DF508/IVS8-7T/9T	1		
DF508/394delTT	1		
c.325_327delinsG p.(Tyr109Glyfs*4) -Heterozygot	1		
DF508/C276X	2		
DF508/CFTR dele17b,18	1		
homozygous polymorphism *	1		
DF508/377G>A in exon 14	2		
457TAT->G/3849G->A	1		
621+1G->T/Q220X	1		
N1303K/394 del TT	1		
c.2501_2052delAAinsG/c.3718-2477c>t	2		
W1282X/394delTT	2		
c.DNA:5466X/R1070Q	1		

* homozygous polymorphism: c.1408G>A homozygous, c.1680-870T>A homozygous, c.1680-784T>G homozygous, c.2562T>G homozygous, c.2909-92G>A homozygous, c.3368-140A>C homozygous, c.3469-65C>A homozygous, c.4389G>A homozygous.

Discussion

In this prospective cross-sectional study, we found that hepatic disease in children with CF was not significantly associated with major CFTR genotypes, including the DF508/DF508 mutation, which was the most prevalent genotype in our cohort. The cumulative incidence analysis suggested a slight delay in CF diagnosis among patients who developed hepatic disease. This observation highlights the genetic heterogeneity within our CF population, with a predominance of the DF508 mutation but also a notable presence of less common or unclassified mutations.

Our findings contribute to the ongoing debate regarding the relationship between CFTR genotypes and hepatic disease in CF patients. While severe CFTR mutations, such as DF508/DF508, are traditionally associated with more severe clinical manifestations including pancreatic insufficiency and respiratory complications, their link to liver disease remains less definitive [14-17]. Several studies have investigated this relationship with varying results. For example, research involving Turkish children with CF indicated that while severe CFTR mutations were linked to markers of disease

severity such as pancreatic insufficiency and chronic lung infections, a direct connection to liver disease was not clearly established [17]. Similarly, studies focusing on CF patients with severe liver disease who were ineligible for CFTR modulators did not find a direct correlation between specific CFTR mutations and liver disease severity [18]. These findings suggest that factors beyond the CFTR genotype, such as environmental influences or other genetic modifiers, may play a more critical role in the development of liver disease in CF patients.

Additionally, reviews of CF-related liver disease have underscored the complexity of its pathophysiology, proposing that while CFTR mutations contribute to the condition, other mechanisms, such as biliary obstruction and immune modulation, are also involved [19-21].

This complexity may explain the lack of significant association between major CFTR genotypes and hepatic disease in our study. Our results underscore the need for further research to elucidate additional genetic and environmental factors that may contribute to liver disease in CF.

***SERPINA* genotypes**

Investigating *SERPINA1* genotypes in the context of CF is crucial for elucidating genetic modifiers that influence disease progression, particularly with respect to liver involvement. CF primarily results from mutations in the *CFTR* gene, with the F508del (DF508) mutation being the most prevalent. This mutation manifests in various genotypic combinations, including DF508/DF508, DF508/Others, and Others/Others, each of which can differentially impact the clinical severity of CF [22,23]. Specifically, the homozygous DF508/DF508 genotype is commonly associated with more severe CF symptoms compared to heterozygous combinations [22].

Beyond *CFTR* mutations, the *SERPINA1* gene, which encodes alpha-1 antitrypsin, plays a significant role in the development of CFLD. The SERPINA1 Z allele (C/T vs. C/C) is particularly significant due to its association with abnormal protein folding and the accumulation of misfolded proteins specifically in the endoplasmic reticulum of hepatocytes. This accumulation can exacerbate hepatic complications. Evidence suggests that CF patients carrying the SERPINA1 Z allele are at a heightened risk of developing CFLD [8,19,24]. Additionally, the SERPINA1 S allele (A/T vs. T/T), although less extensively studied, may also influence liver disease risk in CF patients [11,25].

Research consistently demonstrates that the presence of SERPINA1 alleles, especially the Z allele, correlates with more severe CFLD. This underscores the importance of incorporating *SERPINA1* genetic screening alongside *CFTR* mutation analysis to better predict and manage liver disease in CF patients [26]. Understanding these genetic interactions is essential for developing targeted therapies and improving patient outcomes. Comprehensive genotypic analysis, encompassing both *CFTR* and *SERPINA1* variants, is vital for advancing personalized treatment approaches and optimizing care for CF patients [19].

The pathophysiological relationship between the *SERPINA1* gene and liver disease centers on the alpha-1 antitrypsin (AAT) protein, which is encoded by this gene. The Z allele of *SERPINA1* produces a defective variant of AAT, known as ATZ, which is prone to misfolding and polymerization. This misfolded protein accumulates in the endoplasmic reticulum of hepatocytes, leading to cellular stress and liver damage through a toxic gain-of-function mechanism [25-29]. The accumulation of ATZ induces endoplasmic reticulum stress and activates pathways such as the c-Jun N-terminal kinase (JNK) pathway, exacerbating proteotoxicity and contributing to liver injury [30]. Additionally, the retention of ATZ within the liver reduces the availability of functional AAT in the bloodstream, potentially impacting lung function due to AAT's role in inhibiting neutrophil elastase [28,31]. The pathogenesis of liver disease in alpha-1 antitrypsin deficiency is complex, involving multiple cellular responses such as apoptosis and inflammation, driven by the toxic effects of ATZ accumulation in liver cells [30-32]. Understanding these mechanisms is essential for developing targeted therapies to mitigate liver damage in patients with AAT deficiency.

Limitations

This study has several limitations that must be considered. The cross-sectional design restricts our ability to establish causal relationships between genetic factors and the development of hepatic disease in CF patients. The relatively small sample size, particularly among those with hepatic disease, limits the statistical power to detect significant associations, especially for rare CFTR mutations and SERPINA1 alleles. Additionally, the presence of unclassified genotypes introduces further uncertainty, complicating the interpretation of genotype-phenotype relationships. The observational nature of the study also means that confounding factors cannot be entirely excluded.

Strengths

This study has several notable strengths that enhance its contribution to understanding hepatic disease in children with CF, particularly as it is the first of its kind conducted in Romania. The cross-sectional design enabled systematic and comprehensive collection of clinical and genetic data, thereby enhancing the reliability of the findings. The study's inclusion of a well-characterized cohort with detailed phenotypic and genotypic information provided valuable insights into the relationship between specific CFTR mutations, SERPINA1 alleles, and hepatic disease. Furthermore, the study's examination of a wide range of CFTR genotypes, including rare and unclassified mutations, adds significant depth to our understanding of the genetic diversity in CF.

Clinical implications

The clinical implications of this study are

substantial, particularly for the management of children with CF in Romania. The findings emphasize the necessity of regular liver function monitoring and early identification of hepatic complications in CF patients, irrespective of their genotype. As the first study in Romania to address this issue, it establishes a critical foundation for future research and offers valuable insights that can inform clinical practice and guide further investigations in this population.

Conclusions

This study offers valuable insights into the interplay between CFTR genotypes, SERPINA1 alleles, and hepatic disease in children with CF, representing the first investigation of its kind in Romania. Although no significant association was found between specific CFTR genotypes and hepatic complications, our findings underscore the critical importance of early diagnosis and the use of fibrosis markers to identify children at risk for liver involvement. The study highlights the necessity for vigilant monitoring of liver function in CF patients and suggests that a personalized approach to treatment, taking into account the observed genetic diversity, may enhance patient care. Continued research is essential to further elucidate the genetic and environmental factors contributing to hepatic disease in CF, aiming to refine management strategies and improve patient outcomes.

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