SYSTEMATIC REVIEW

DOI: http://dx.doi.org/10.15403/jgld-5879

Impact of CFTR Modulator Therapies on Liver Function in Cystic Fibrosis Patients: A Systematic Review of Hepatic Biomarkers

Elena-Simona Moiceanu[1], Daniel-Corneliu Leucuța[2], Viorela Gabriela Nițescu[3], Andreea Lescaie[3], Maria Iacobescu[4], Iustina Violeta Stan[5], Simona Elena Moșescu[6], Iolanda Cristina Vivisenco[7], Dan Lucian Dumitrașcu[8]

1) Pediatric Poison Centre, Grigore Alexandrescu Clinical Emergency Hospital for Children, Bucharest; Iuliu Hațieganu University of Medicine and Pharmacy, Cluj-Napoca; 2) Medical Informatics and Biostatistics Dept, Iuliu Hațieganu University of Medicine and Pharmacy, Cluj-Napoca; 3) Pediatric Poison Centre, Grigore Alexandrescu Clinical Emergency Hospital for Children, Bucharest; Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; 4) Institute of Medical Research and Life Sciences – MEDFUTURE, Iuliu Hațieganu University of Medicine and Pharmacy, Cluj-Napoca; 5) Alessandrescu-Rusescu National Institute for Mother and Child Health, Bucharest; Carol Davila University of Medicine and Pharmacy, Bucharest; 6) Alessandrescu-Rusescu National Institute for Mother and Child Health, Bucharest; 7) Dept. of Pediatrics, Grigore Alexandrescu Clinical Emergency Hospital for Children, Bucharest; Carol Davila University of Medicine and Pharmacy, Bucharest; 8) 2nd Dept. of Internal Medicine, Emergency Clinical County Hospital, Cluj-Napoca; Iuliu Hațieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Address for correspondence:
Daniel-Corneliu Leucuța
Medical Informatics and Biostatistics Dept, Iuliu Hațieganu University of Medicine and Pharmacy, Cluj-Napoca; dleucuta@umfcluj.ro

Received: 01.08.2024
Accepted: 05.09.2024

ABSTRACT

Background & Aims: Cystic fibrosis transmembrane conductance regulator (CFTR) modulators, including elexacaftor/ivacaftor/tezacaftor (ETI) and lumacaftor/ivacaftor (LI), have revolutionized the treatment of cystic fibrosis. However, their impact on liver function remains unclear, with varying effects reported across studies. The aim of this study was to systematically review the effects of CFTR modulators on liver function in cystic fibrosis patients by evaluating changes in key hepatic biomarkers.

Methods: A comprehensive literature search was conducted in Europe PubMed Central and PubMed databases for studies published between January 1, 2010, and December 31, 2023. Eligible studies included those assessing the impact of CFTR modulators on liver biomarkers in cystic fibrosis patients. Meta-analyses were performed where possible.

Results: Six studies encompassing 195 patients were included, with significant heterogeneity in study design, population, and outcomes. The review found mixed results for alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyltransferase (GGT) levels, with some studies reporting increases and others decreases. LI therapy was associated with significant reductions in GGT and alkaline phosphatase (AP) levels, while ETI therapy showed significant increases in bilirubin levels. Albumin levels increased significantly with both therapies.

Conclusions: CFTR modulators have varying effects on liver function biomarkers in cystic fibrosis patients, with LI therapy generally showing more favorable outcomes on liver health. The significant heterogeneity among studies underscores the need for more standardized research to better understand these effects and guide clinical management.

Key words: cystic fibrosis – CFTR modulators – liver function – ALT – AST – GGT – AP – bilirubin – albumin – systematic review.

Abbreviations: ALT: alanine aminotransferase; AP: alkaline phosphatase; APRI: aspartate aminotransferase-to-platelet ratio index AST: aspartate aminotransferase; CF: cystic fibrosis; CFLD: liver involvement in CF; CFTR: CF transmembrane conductance regulator; ETI: elexacaftor/ivacaftor/tezacaftor; GGT: gamma glutamyltransferase; LI: lumacaftor/ivacaftor.

INTRODUCTION

Cystic fibrosis (CF) is an inherited, life-limiting autosomal recessive disorder characterized by mutations in the CF transmembrane conductance regulator (CFTR) gene, which leads to defective chloride transport across epithelial cells. This causes thick, sticky mucus to accumulate in various organs, primarily the lungs, pancreas, and liver [1, 2]. The buildup of mucus in these organs leads to inflammation, chronic infections, and organ damage. Cystic fibrosis affects multiple systems in the body and is considered one of the most common lethal genetic diseases in the Caucasian population [2].

It is estimated that over 160,000 individuals are living with CF across 94 countries. Of these, approximately 65% have been diagnosed, and 12% are receiving triple combination therapy. More than 50,000 individuals are believed to have undiagnosed CF. However, the accuracy of these estimates is limited, particularly in low- and middle-income countries, due to a scarcity of high-quality data [3].

Mortality associated with CF has significantly improved due to advancements in treatments [4]. However, respiratory

complications and organ damage still lead to high morbidity and mortality rates in affected patients [5]. Liver involvement in cystic fibrosis (CFLD) is the third leading cause of death in CF patients [6, 7], accounting for 2.5% of overall mortality [8].

As life expectancy increases, the prevalence of liver complications also rises [9]. Liver involvement in cystic fibrosis presents in a variety of forms, with the most severe being multilobular cirrhosis, which develops in approximately 5-10% of patients. The prevalence of CFLD is around 23% [10]. The fibrosis and subsequent cirrhosis often lead to complications such as portal hypertension, esophageal varices, and liver failure [11]. Until now, no treatment is known to prevent and manage the advanced forms of CFLD [12].

Cystic fibrosis has transitioned into an era of variant-specific therapies, which are tailored to the specific genetic variants in the CFTR gene [13]. The development of CFTR modulators, specifically elexacaftor /tezacaftor /vacaftor (ETI) and lumacaftor /ivacaftor (LI), has revolutionized the treatment of cystic fibrosis [14]. These therapies target the underlying defect of CFTR mutations, enhancing the protein's function and improving clinical outcomes, especially in pulmonary and gastrointestinal manifestations of the disease [15]. The ETI combination has been shown to significantly improve lung function, decrease pulmonary exacerbations, and enhance overall quality of life [13].

Although CFTR modulators primarily target respiratory symptoms, their effects on liver function are also noteworthy [16]. However, the long-term effects of these therapies on hepatic biomarkers remain an area of ongoing research [15].

The aim of this study was to systematically review the impact of CFTR modulators, specifically ETI and LI, on liver function in cystic fibrosis patients. This review evaluated changes in key hepatic biomarkers, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltransferase (GGT), bilirubin, alkaline phosphatase (AP), albumin levels, and AST-to-platelet ratio index (APRI), to identify clinical patterns and implications associated with these therapies.

METHODS

Search Strategy

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [17]. A comprehensive literature search was performed using two databases: Europe PubMed Central and PubMed. The search strategy was designed to identify studies published between January 1, 2010, and December 31, 2023, investigating the effects of cystic fibrosis modulators on liver function. The search terms used were: „cystic fibrosis AND liver AND modulators." In Europe PubMed Central, the search was performed using the query: cystic fibrosis AND liver AND modulators AND (FIRST_PDATE: [2010-01-01 TO 2023-12-31]). In PubMed, the query was cystic fibrosis AND liver AND modulators AND („2010/01/01":"2023/12/31"[PDAT]).

Eligibility Criteria

The following PICOS strategy for inclusion of studies was used: 1) population - patients with cystic fibrosis; 2) intervention - cystic fibrosis transmembrane conductance regulator (CFTR) modulators, including ETI or LI; 3) outcomes - studies reporting changes in liver biomarkers such as ALT, AST, GGT, bilirubin, AP, and albumin levels; 4) study design: prospective cohort, retrospective cohort, before-after studies, observational studies.

Exclusion criteria included animal studies, case reports, reviews, mecanicistic studies, conference abstracts, and editorials. No restrictions on language were applied.

Information Sources

The literature search was conducted in June, 2024, using Europe PubMed Central and PubMed databases. References from included articles were also screened to identify any additional relevant studies.

Study Selection

Two independent reviewers screened the titles and abstracts of the search results (E.S.M. and A.L.). Full texts of potentially eligible studies were retrieved and assessed for inclusion based on the pre-defined eligibility criteria. Any disagreements between reviewers were resolved through discussion.

Data Extraction

The following information was collected: study characteristics: country, study design, duration of follow-up, number of participants, patient age, and sex distribution, type of CFTR modulator used (ETI or LI), outcomes: baseline and post-treatment levels of liver biomarkers (ALT, AST, GGT, bilirubin, AP, albumin, APRI), and statistical significance of changes in these biomarkers. Data was extracted by two authors (E.S.M. and D.C.L.), in case of inadvertences the original article was verified.

Data Synthesis and Analysis

Due to the heterogeneity of the included studies, a qualitative synthesis of most of results was performed. Where possible, meta-analyses were conducted using a random-effects model using restricted maximum likelihood, to calculate pooled effect sizes and 95% confidence intervals (CIs). The effect size was the mean of change before and after therapy in liver biomarkers. In case necessary statistics were unavailable (i.e. standard deviation), they were computed using formulas from Wan et al. [18]. The I^2 statistic was used to assess heterogeneity between studies. The Cochrane Collaboration suggestions for heterogeneity classifications were used: 0-40%: might not be important; 30-60%: moderate heterogeneity; 50-90%: substantial heterogeneity; 75-100%: considerable heterogeneity [19]. Sensitivity analyses were performed using a leave-one-out approach to assess the robustness of the findings. Statistical analyses were performed using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) [20] and the meta R package [21]. The publication bias assessment was not possible due to the limited number of included studies.

RESULTS

The selection process is detailed in the PRISMA flowchart (Fig. 1). First 2,399 records from database searches were

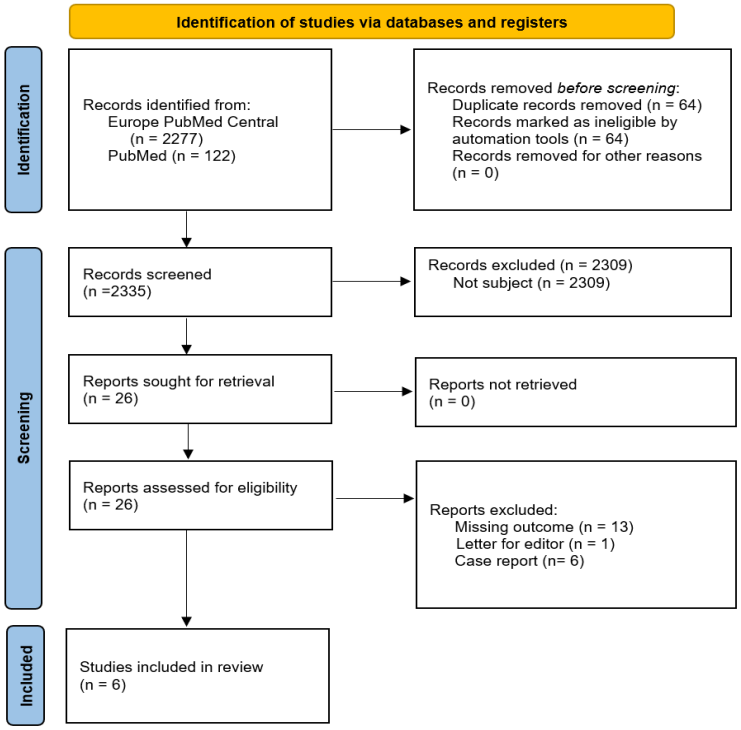

Fig. 1. PRISMA flowchart.

identified, including 2,277 from Europe PubMed Central and 122 from PubMed. Before screening, 64 duplicate records were removed, leaving 2,335 records for selection. During the screening process of titles and abstracts, 2,309 records were excluded for not being relevant to the subject, resulting in 26 reports sought for full-text retrieval, all of which were successfully retrieved. Of these, 13 reports were excluded for missing outcomes, 1 was excluded as a letter to the editor, and 6 were excluded as case reports. Ultimately, 6 studies were included in the final review [22-27].

The selected for the review included a total of 195 patients.

Studies Characteristics

The characteristics of the studies are presented in Tables I and II. All studies were carried out in Europe, three in Italy and one in each of the following Germany, France, United Kingdom. The study designs were prospective, retrospective, before-after. The follow up was from 6 months to 36 months, the most frequent follow up being of 12 months. The patients in the studies were young. The distribution based on sex is balanced, for most of the studies. Four studies (67%) had adults as study group, one study (17%) focused on children, and one (17%) had two groups one of children and one of adults. Half of the studies used ETI as therapy and the other half used LI. Three studies (50%) were on homozygote patients, one (17%) on heterozygote patients, and the other two (33%) were on homozygote and heterozygote patients.

Evolution of Hepatic Biomarkers under Cystic Fibrosis Therapies

The results for ALT and AST levels varied across studies, with some showing increases and others showing decreases, some of them significant, and some without reaching the level of significance (Table II). No clear pattern could be distinguished regarding the tendencies in relation to the characteristics of the studies.

The results for GGT levels varied across studies too, with some showing increases and others showing decreases (Table III). Two studies showed statistically significant decreases, an observation that might suggest that LI therapy may improve

Table I. Studies' characteristics

Study name	Country	Study design	Time (months)	N	Age (years)	Female (%)
Schnell, 2023	Germany	Prospective cohort	6	20	24.1 (10.9)	25
Carnovale, 2022	Italy	Observational cohort	12	20	31.9 (7.7)	60
Drummond, 2022	France	Retrospective cohort	12	28	14.4(13.0 – 16.2)	46
Gelzo, 2020	Italy	Before-after design	15 (6)	20	27 (7)	48
Castaldo, 2024	Italy	Before-after design	12-36	33	24 (20-30)	50
Tewkesbury, 2024	United Kingdom	Retrospective cohort	21(17-25)	74	>18	46

Quantitative data is presented as mean (standard deviation) or median (interquartile range); -, not reported.

Table II. Evolution of AST and ALT in the selected studies

Study name	Time (months)	N	Age group	Therapy	Genotype	ALT (U/L)				M diff.	p	AST (U/L)				M diff.	p
						Before		After				Before		After			
						M	SD	M	SD			M	SD	M	SD		
Schnell, 2023	6	10	Children	ETI	HM/HT	27.0	11.1	33.1	19.4	6.1	0.080	27.7	16.1	31.1	19.5	3.4	0.280
Schnell, 2023	6	10	Adult	ETI	HM/HT	22.7	7.8	21.8	1.0	-0.9	0.720	29.8	13.4	26.2	10.0	-3.6	0.420
Carnovale, 2022	12	20	Adult	ETI	HT	20.6	9.4	28.5	18.4	7.9	<0.05	21.0	13.6	33.2	21.9	12.2	<0.05
Drummond, 2022	12	28	Children	LI	HM	34.7	12.5	27.3	9.4	-7.3	0.010	32.0	15.6	23.7	12.5	-8.3	0.020
Gelzo, 2020	15 (6)	20	Adult	LI	HM	20.7	4.7	21.3	10.2	-	-	21.0	6.4	23.3	9.6	-	-
Castaldo, 2024	12	33	Adult	LI	HM	-	-	-	-	-	-	23.3	9.3	20.7	11.6	-2.7	<0.05
Tewkesbury, 2024	21 (17-25)	74	Adult	ETI	HM/HT	26.3	9.1	27.3	9.8	1.0	0.870	-	-	-	-	-	-

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ETI: elexacaftor/tezacaftor/ivacaftor; LI: lumacaftor/ivacaftor; M: mean; diff: difference; SD: standard deviation; HM: homozigote; HT: heterozygote; -: not reported.

GGT levels in certain populations, while ETI therapy showed mixed results (without reaching the significance levels).

The total bilirubin levels showed statistically significant increases in studies using ETI therapy in the two studies where they were reported (Table III). In contrast, under LI therapy the total bilirubin levels significantly declined in the two studies where they were reported. A similar pattern was observed for the direct bilirubin levels. There were significant increases under the ETI therapy, and significant decreases under the LI therapy.

Two studies involving LI therapy show significant redctions in AP levels, suggesting an improvement in liver function (Table IV). In contrast, ETI therapy, in one study, was associated with an increase in AP levels, albeit not statistically significant. Albumin levels had a statistically significant increase in two studies, one using LI therapy and the other using ET therapy (Table IV). ETI therapy was associated with a slight statistically significant decrease in APRI, while LI therapy was associated with a slight statistically significant increase in APRI (Table IV).

Due to the high heterogeneity between the study results, with significant but contrary results, the meta-analyses could not be carried out for most of the biomarkers.

Only for AST/ALT and albumin levels the meta-analyses results could be obtained (Table V). Concerning AST/ALT the meta-analysis was performed on the two cohorts of Schnell, 2003, study that showed a non-significant increase.

The meta-analysis of the two studies presenting data on albumin levels showed a significant increase in albumin levels (Table V). As expected, the leave-one-out sensitivity analyses offered significant results no matter which study was excluded.

DISCUSSION

This review synthesized data from six studies encompassing 195 patients, all conducted in Europe. We focused on the effects of cystic fibrosis therapies, primarily ETI and LI, on hepatic biomarkers. The transaminases levels showed inconsistent changes across the studies, with conflicting pattern regarding increases or decreases. Gamma glutamyltrasferase levels followed a similarly varied pattern, though significant decreases were observed in studies utilizing LI therapy, suggesting potential benefits of this treatment in reducing GGT levels. In contrast, ETI therapy presented mixed results without reaching statistical significance. The total and direct bilirubin levels exhibited a more consistent pattern: significant increases were noted in studies using ETI therapy, while LI therapy was associated with significant decreases. This dichotomy suggests possible differing impacts of these therapies on bilirubin metabolism. AP levels showed improvement under LI therapy,

Table III. Evolution of GGT, total and direct bilirubin in the selected studies

Study name	GGT (U/L)						Total bilirubin (mg/dL)						Direct bilirubin (mg/dL)					
	Before		After				Before		After				Before		After			
	M	SD	M	SD	M diff.	p	M	SD	M	SD	M diff.	p	M	SD	M	SD	M diff.	p
Schnell, 2023	35.1	46.6	49.1	72.7	14.0	0.170	1.0	1.0	1.1	0.7	0.2	0.040	0.6	0.9	0.6	0.7	0.0	0.180
Schnell, 2023	23.2	11.5	23.4	9.1	0.2	0.930	0.6	0.3	0.8	0.4	0.2	0.010	0.3	0.1	0.3	0.2	0.1	0.040
Carnovale, 2022	15.1	8.6	17.6	15.8	2.5	-	0.5	0.3	1.1	0.9	0.6	<0.05	0.2	0.1	0.4	0.3	0.2	<0.05
Drummond, 2022	24.7	22.7	14.3	5.5	-10.3	0.010	0.4	0.2	0.3	0.1	0.0	0.030	-	-	-	-	-	NA
Gelzo, 2020	14.0	6.4	16.0	9.6	-	-	0.6	0.3	0.6	0.3	-	-	0.3	0.1	0.3	0.1	-	NA
Castaldo, 2024	15.3	7.7	14.0	8.5	-1.3	<0.050	0.6	0.3	0.4	0.1	-0.2	<0.05	0.3	0.1	0.2	0.1	-0.1	<0.05
Tewkesbury, 2024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NA

GGT: gamma glutamyltransferase. For the rest of abbreviations see Table II.

Table IV. Evolution of AP, albumin and APRI in the selected studies

	AP (U/L)						Albumin (g/dL)						APRI					
	Before		After				Before		After				Before		After			
Study name	M	SD	M	SD	M diff.	p	M	SD	M	SD	M diff.	p	M	SD	M	SD	M diff.	p
Schnell, 2023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Schnell, 2023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Carnovale, 2022	113.2	49.5	128.7	61.4	15.5	n.s.	4.1	0.6	4.5	0.2	0.5	<0.05	-	-	-	-	-	-
Drummond, 2022	-	-	-	-	-	-	-	-	-	-	-	-	0.4	0.3	0.3	0.2	-0.1	0.010
Gelzo, 2020	108.7	16.0	70.7	19.1	-38.0	0.005	2.4	2.4	2.7	3.2	-	-	-	-	-	-	-	-
Castaldo, 2024	107.3	16.3	70.7	21.7	-36.7	<0.05	4.3	0.2	4.5	0.4	0.2	<0.05	-	-	-	-	-	-
Tewkesbury, 2024	-	-	-	-	-	-	-	-	-	-	-	-	0.3	0.1	0.4	0.2	0.1	0.020

AP: alkaline phosphatase; APRI: aspartate aminotransferase to platelet ratio index; n.s.: not significant. For the rest of abbreviations see Table II.

as evidenced by significant reductions in two studies, whereas ETI therapy was associated with a non-significant increase in AP levels. Albumin levels significantly increased under both therapies, indicating a positive effect on liver synthetic function. Meanwhile, APRI showed opposing trends, with ETI therapy resulting in a slight but significant decrease, and LI therapy leading to a slight significant increase. The meta-analyses were largely constrained by the high heterogeneity across study results, limiting meaningful conclusions to AST/ALT and albumin levels.

Recent study demonstrated that LI improves liver function tests and liver fibrosis indices in patients with pre-existing liver abnormalities. Lumacaftor/ivacaftor may be the first drug capable of reversing CF-associated liver fibrosis; however, larger multicenter studies incorporating imaging and/or histology are needed to confirm these findings [28].

In a recent case series study, it was noted that none of the participants exhibited elevations in ALT or AST exceeding three times the upper limit of normal in conjunction with total bilirubin levels surpassing twice the upper limit of normal. Additionally, no instances of transaminase elevation necessitated interruption or discontinuation of the study drug [29].

Several hypotheses can explain how ETI, and LI may improve hepatic function in patients with CF. These mechanisms focus on restoring the function of the CFTR protein, which plays a vital role in chloride ion transport, impacting multiple organs, including the liver.

One hypothesis might relate to CFTR modulation and hepatic ion transport. CFTR modulators improve chloride and bicarbonate secretion in the liver by correcting defective CFTR channels. This enhances bile flow and reduces bile duct blockages, which are common in CFLD. By improving bile secretion, CFTR modulators like ETI may decrease the risk of bile duct obstructions and cholestasis [30].

Another hypothesis points to reduction of inflammation and fibrosis. ETI therapy has shown to improve biomarkers of liver fibrosis, such as GGT and APRI. This indicates a reduction in liver fibrosis progression. In children treated with LI, reductions in these fibrosis markers were observed, suggesting a potential role in improving liver health by decreasing fibrotic activity in the liver [28].

Improvement in nutrient absorption might constitute another hypothesis. CFTR modulators have been linked to better nutrient absorption, which indirectly improves liver function by enhancing the overall metabolic state. Increased BMI and serum cholesterol levels, as observed in patients treated with ETI, suggest improved lipid metabolism, which is crucial for hepatic function and bile production [25].

A more interesting hypothesis related protection from biliary disease. While ETI has been associated with adverse events such as biliary colic, it may also reduce the incidence of severe liver complications by modulating the CFTR function and improving bile flow, reducing the risk of gallbladder diseases that are prevalent in CF patients [31].

Table V. Meta-analyses results concerning AST/ALT, albumin and GPR mean

Characteristic, effect size type	N studies	Effect size (95% CI)	p-value	I^2 (95% CI)	p-value	Studies	Leave one out
AST/ALT (U/L) mean, MD	2	0.08 (-0.02 - 0.17)	0.117	0	0.641	Schnell, 2023; Schnell, 2023	- Schnell, 2023: 0.09 (-0.02-0.2), p=0.116;
							- Schnell, 2023: 0.04 (-0.14-0.22), p=0.66
Albumin (g/dL) mean, MD	2	0.26 (0.04 - 0.47)	0.019	16.5	0.274	Carnovale, 2022; Castaldo, 2024	- Carnovale, 2022: 0.2 (0.01-0.39), p=0.042;
							- Castaldo, 2024: 0.47 (0.03-0.9), p=0.036
GPR mean after, MD	1	0.19 (-9.34 - 9.72)	0.969	NC		Tewkesbury, 2024	NC

M: mean; MD: mean difference; SD: standard deviation; CI: confidence interval; NA: not applicable; NC: not calculable; I^2: heterogeneity indicator.

Limitations

This review has several limitations that should be acknowledged. First, the included studies showed significant heterogeneity in study design, varying follow-up durations, patient characteristics, genotypes, and the specific biomarkers measured, which limited the ability to perform comprehensive meta-analyses. The small sample sizes diminished the study power. All studies were published in Europe, thus affecting the generalizability of the findings.

Strengths

Despite these limitations, this review also has several strengths. It provides a comprehensive synthesis of the current evidence on the impact of CFTR modulators on liver function, covering numerous hepatic biomarkers across different patient populations. This review also highlights important trends and potential differential effects of ETI and LI therapies on liver biomarkers, offering valuable insights for clinicians and researchers involved in the management of cystic fibrosis.

Clinical Implications

The findings from this review highlight the need for personalized monitoring of liver function in cystic fibrosis patients undergoing ETI or LI therapies. The significant increases in bilirubin levels associated with ETI therapy suggest that clinicians should closely monitor liver enzymes and bilirubin, particularly in patients with existing liver conditions. Conversely, LI therapy's consistent improvements in GGT and AP levels may make it a preferable option for patients with liver concerns. Regular liver function assessments are crucial to ensure the safety and efficacy of these treatments, and treatment protocols should be adjusted based on individual patient responses.

CONCLUSIONS

This review highlights the complex and varied impacts of cystic fibrosis therapies, specifically ETI and LI, on hepatic biomarkers. The findings from six studies involving 195 patients demonstrate significant heterogeneity, with mixed results observed across key markers such as ALT, AST, GGT, bilirubin, AP, and albumin levels. Notably, LI therapy showed a more consistent trend toward improving liver function, as evidenced by significant reductions in GGT and AP levels, and decreases in bilirubin levels, while ETI therapy was associated with increases in bilirubin levels and a non-significant rise in AP levels.

Conflicts of interest: None to declare.

Authors' contribution: E.S.M., D.C.L., V.G.N., A.L. and D.L.D. conceived the study. E.S.M., I.V.S., S.E.M., D.C.L.,V.G.N., I.C.V., A.L. and D.L.D. designed the methodology. D.C.L. performed the literature search E.S.M., I.V.S., S.E.M., D.C.L., M.I., I.C.V. and D.L.D. analyzed the literature and interpreted the data. E.S.M. drafted the manuscript. E.S.M, D.C.L., I.V.S., S.E.M., M.I., V.G.N., I.C.V., A.L. and D.L.D. revised the manuscript. I.V.S., S.E.M., V.G.N., D.-C.L. and D.L.D. supervised the project. All authors have read and agreed to the published version of the manuscript.

REFERENCES

1 Quinton PM. Cystic fibrosis: impaired bicarbonate secretion and mucoviscidosis. Lancet 2008;372:415–417. doi:10.1016/S0140-6736(08)61162-9

2. Elborn JS. Cystic fibrosis. Lancet 201;388:2519–253. doi:10.1016/S0140-6736(16)00576-6

3. Guo J, Garratt A, Hill A. Worldwide rates of diagnosis and effective treatment for cystic fibrosis. J Cyst Fibros 2022;21:456-462. doi:10.1016/j.jcf.2022.01.009

4. O'Sullivan BP, Freedman SD. Cystic fibrosis. Lancet 2009;373:1891–1904. doi:10.1016/S0140-6736(09)60327-5

5. Turcios NL. Cystic fibrosis lung disease: An overview. Respir Care 2020;65:233-251. doi:10.4187/respcare.06697

6. Herrmann U, Dockter G, Lammert F. Cystic fibrosis-associated liver disease. Best Pract Res Clin Gastroenterol 2010;24:585-592. doi:10.1016/j.bpg.2010.08.003

7. Sakiani S, Kleiner DE, Heller T, Koh C. Hepatic Manifestations of Cystic Fibrosis. Clin Liver Dis 2019;23:263-277. doi:10.1016/j.cld.2018.12.008

8. Colombo C. Liver disease in cystic fibrosis. Curr Opin Pulm Med 2007;13:529-536. doi:10.1097/MCP.0b013e3282f10a16

9. Moyer K, Balistreri W. Hepatobiliary disease in patients with cystic fibrosis. Curr Opin Gastroenterol 2009;25:272-278. doi:10.1097/MOG.0b013e3283298865

10. Wasuwanich P, Karnsakul W. Cystic fibrosis-associated liver disease in children. Minerva Pediatr 2020;72:440-447. doi:10.23736/S0026-4946.20.05895-8

11. Wasuwanich P, Karnsakul W. Cystic fibrosis-associated liver disease in children. Minerva Pediatr 2020;72:440-447. doi:10.23736/S0026-4946.20.05895-8

12. Palaniappan SK, Than NN, Thein AW, Moe S, van Mourik I. Interventions for preventing and managing advanced liver disease in cystic fibrosis. Cochrane Database Syst Rev 2017;8:CD012056. doi:10.1002/14651858.CD012056.pub3

13. Southern KW, Castellani C, Lammertyn E, et al. Standards of care for CFTR variant-specific therapy (including modulators) for people with cystic fibrosis. J Cyst Fibros 2023;22:17-30. doi:10.1016/j.jcf.2022.10.002

14. Eldredge JA, Oliver MR, Ooi CY. Cystic fibrosis liver disease in the new era of cystic fibrosis transmembrane conductance regulator (CFTR) modulators. Paediatr Respir Rev 2024;50:54-61. doi:10.1016/j.prrv.2023.12.005

15. Staufer K. Current treatment options for cystic fibrosis-related liver disease. Int J Mol Sci 2020;21:8586. doi:10.3390/ijms21228586

16. Fiorotto R, Strazzabosco M. Pathophysiology of Cystic Fibrosis Liver Disease: A Channelopathy Leading to Alterations in Innate Immunity and in Microbiota. Cell Mol Gastroenterol Hepatol 2019;8:197-207. doi:10.1016/j.jcmgh.2019.04.013

17. Page MJ, McKenzie JE, Bossuyt PM, et al. "The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi:10.1136/bmj.n71

18. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135. doi:10.1186/1471-2288-14-135

19. Higgins JP, Li T, Deeks JJ. Choosing effect measures and computing estimates of effect. In: Higgins JP, Thomas J, Chandler J, et al. (Eds.). Cochrane Handbook for Systematic Reviews of Interventions. Second edition. Wiley; 2019:143–176. doi:10.1002/9781119536604.ch6

20. R Core Team. A Language and Environment for Statistical Computing. R Foundation for Statistical Computing: Vienna, Austria. Found Stat Comput Vienna Austria; 2024.
21. Schwarzer G, Carpenter JR, Rücker G. Meta-Analysis with R. Cham: Springer International Publishing Switzerland; 2015.
22. Schnell A, Jüngert J, Klett D, et al. Increase of liver stiffness and altered bile acid metabolism after triple CFTR modulator initiation in children and young adults with cystic fibrosis. Liver Int 2023;43:878–887. doi:10.1111/liv.15544
23. Carnovale V. Scialo F, Gelzo M, et al. Cystic Fibrosis Patients with F508del/Minimal Function Genotype: Laboratory and Nutritional Evaluations after One Year of Elexacaftor/Tezacaftor/Ivacaftor Treatment. J Clin Med 2022;11:6900. doi:10.3390/jcm11236900
24. Drummond D, Dana J, Berteloot L, et al. Lumacaftor-ivacaftor effects on cystic fibrosis-related liver involvement in adolescents with homozygous F508 del-CFTR. J Cyst Fibros 2022;21:212-219 doi:10.1016/j.jcf.2021.07.018
25. Gelzo M, Iacotucci P, Caputo M, et al. Lumacaftor/ivacaftor improves liver cholesterol metabolism but does not influence hypocholesterolemia in patients with cystic fibrosis. J Cyst Fibros 2021;20:e1-e6. doi:10.1016/j.jcf.2020.06.015
26. Castaldo A, Gelzo M, Iacotucci P, et al. One year of treatment with elexacaftor/tezacaftor/ivacaftor in patients with cystic fibrosis homozygous for the F508del mutation causes a significant increase in liver biochemical indexes. Front Mol Biosci 2024;10:1327958. doi:10.3389/fmolb.2023.1327958
27. Tewkesbury DH, Scott J, Barry PJ, et al. Effects of elexacaftor/tezacaftor/ivacaftor on liver fibrosis markers in adults with cystic fibrosis. J Cyst Fibros 2024;23:349-353. doi:10.1016/j.jcf.2023.09.006
28. Levitte S, Fuchs Y, Wise R, Sellers ZM. Effects of CFTR modulators on serum biomarkers of liver fibrosis in children with cystic fibrosis. Hepatol Commun 2023;7:e0010. doi:10.1097/HC9.0000000000000010
29. Heijerman HGM, McKone EF, Downey DG, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. Lancet 2019;394:1940-1948. doi:10.1016/S0140-6736(19)32597-8
30. Cohn JA, Strong TV, Picciotto MR, Nairn AC, Collins FS, Fitz JG. Localization of the cystic fibrosis transmembrane conductance regulator in human bile duct epithelial cells. Gastroenterology1993;105:1857-1964. doi:10.1016/0016-5085(93)91085-v
31. Safirstein J, Grant JJ, Clausen E, Savant D, Dezube R, Hong G. Biliary disease and cholecystectomy after initiation of elexacaftor/ivacaftor/tezacaftor in adults with cystic fibrosis. J Cyst Fibros 2021;20:506-510. doi:10.1016/j.jcf.2020.07.014