Received: 29 September 2022 | Revised: 29 December 2022 | Accepted: 16 January 2023

DOI: 10.1002/hsr2.1086

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Gamma-glutamyl transferase and disease course in pediatric-onset primary sclerosing cholangitis: A single-center cohort study

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Abstract

Background and Aims: Patients with pediatric-onset primary sclerosing cholangitis (PSC) are at risk of developing hepatic complications with liver transplantation as only curative treatment. Complications usually occur over many years, underlining the need for reliable surrogate markers to predict the clinical course. Recently, gamma-glutamyl transferase (GGT) has been suggested to allow prediction of the clinical course. In a single-center cohort study, we tested the potency of GGT in this respect.

Methods: We used longitudinal data of patients from our academic center, diagnosed with pediatric-onset PSC between 2000 and 2020. Patients with a GGT decrease from baseline >25% ($n = 36$) were compared with those who did not have this decrease ($n = 7$). We performed Kaplan–Meier analysis and log-rank testing to assess the occurrence of portal hypertensive or biliary complications, hepatobiliary malignancies, liver transplantation, or death.

Results: The median age diagnosis was 15.2 years and 12.1 years in the group with ≤25% decrease of GGT and the group with >25% decrease, respectively ($p = 0.078$). The probability of developing ≥1 complications in the first 5 years after diagnosis was 50% in the group with ≤25% decrease of GGT and 20% in the group with >25% decrease of GGT ($p = 0.031$). The use of medication was not associated with the development of complications.

Conclusion: In a retrospective cohort study, we report that a GGT decrease of >25% within 1 year of diagnosis of pediatric-onset PSC is associated with a lower occurrence of complications within 5 years. Our results provide further support for the recently hypothesized predictive value of first-year GGT change in predicting the disease course in pediatric-onset PSC.

KEYWORDS
autoimmune hepatitis, clinical outcomes, hepatic complications, liver transplantation, surrogate marker

1 | INTRODUCTION

Primary sclerosing cholangitis (PSC) is a rare progressive liver disease with a chronic course, characterized by the destruction of the intra- and extrahepatic bile ducts. The cause of PSC is unknown, but its development and progression have been associated with genetic and environmental factors.[1,2] As of yet, there is no effective treatment to stop or mitigate disease progression in PSC patients.[3]

Phenotypical classification of PSC is based on cholangiography using high-quality magnetic resonance cholangiopancreatography (MRCP) and on histology. Patients with abnormalities on cholangiography are classified as having large duct disease.[3,4] Patients with fibrosing cholangiopathy on histology, but without cholangiographic abnormalities, are usually classified as having "small duct disease." PSC can coexist with autoimmune hepatitis (AIH), which is more frequently recognized in children compared with adults (33% vs. 7%).[5,6] This condition has been described as overlap syndrome based on the frequent concurrence of increased levels of autoantibodies, transaminases, and hypergammaglobulinemia.[5] These patients usually respond to steroids, at least biochemically.[7] PSC has a strong association with inflammatory bowel disease (IBD). Around 70% of all patients with PSC have or will develop IBD, with ulcerative colitis (UC) being the most reported type of IBD associated with PSC.[4] Conversely, in a prospective Canadian registry of children diagnosed with UC or IBD-unclassified, the risk of developing PSC was around 9%.[4]

Patients already diagnosed with IBD who develop PSC typically present with asymptomatic liver test abnormalities. Irrespective of the coexistence of IBD, PSC commonly progresses over time, ultimately evolving to biliary strictures with or without recurrent cholangitis, biliary cirrhosis, and end-stage liver disease.[1] Within 10 years of PSC diagnosis, 50% have developed complications such as biliary strictures or portal hypertension, leading to esophageal varices or ascites. Thirty percent of the patients with childhood-onset PSC will eventually undergo a liver transplantation.[3] Approximately, 1 in 20 liver transplantations in adults are performed for PSC.[8] Recurrence of PSC occurs in 10%–25% of the transplanted patients.[4,9] The relatively slow disease progression of PSC has prompted the search for reliable surrogate markers to predict clinical outcomes. In adult patients with PSC, liver enzymes such as gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) have been evaluated as surrogate endpoints for clinical trials and are recognized as prognostic factors, especially ALP.[2,3,10,11] Adult patients in whom serum ALP decreased to <1.5 times the upper limit of normal (ULN) had a more favorable outcome.[10,11] Since in pediatric patients, ALP is frequently elevated due to nonhepatic causes, such as rapid growth or vitamin D deficiency, GGT has been regarded as a more reliable marker for injury to biliary epithelium.[12]

In a retrospective cohort study of pediatric PSC patients with elevated GGT at diagnosis, Deneau et al. described that normalization of GGT (i.e., <50 IU/L) and/or a percentage decrease of >25% within the first year predicted a favorable 5-year outcome.[3,13] This observation suggested the potency of GGT change in the first year after diagnosis to predict long-term outcomes in pediatric-PSC patients.

In this study, we set out to validate these findings in an independent patient cohort. We tested the hypothesis that a GGT decrease of at least 25% in the first-year postdiagnosis is associated with a more favorable outcome in the first 5 years.

2 | METHODS

2.1 | Study design and setting

We performed a retrospective longitudinal cohort study, carried out at the University Medical Center Groningen (UMCG) in the Netherlands, which is a tertiary care hospital for children with liver disease. We reviewed medical records of patients with pediatric-onset PSC treated at the UMCG and designed an online data registry using the Research Electronic Data Capture (REDCap) to enter longitudinal data. All patients were anonymized during data entry and received an identification number.

2.2 | Ethical approval

The Ethical Review Board of the Erasmus MC in Rotterdam, who assessed the initial study protocol on pediatric PSC patients conducted by Joose et al.,[5] waived the need for informed consent due to the anonymous and noninterventional fashion of the study. For the present study, we obtained secondary approval from the Ethical Review Board of the UMCG.

2.3 | Study population

In this single-center retrospective cohort study, we used a convenience sampling of patients in whom PSC—with or without features of AIH—had been diagnosed before the age of 18 years, between 2000 and 2020. The diagnosis of PSC was based on the biochemical profile (elevation of GGT, elevated conjugated bilirubin levels, or both) with either bile duct irregularities on imaging (MRCP or endoscopic retrograde cholangiopancreatography [ERCP]) or abnormal liver histology characteristic for PSC.[3,5] The presence of bile duct irregularities on cholangiography classified patients as having large duct PSC, whereas a normal cholangiogram in combination with histopathological findings supporting PSC classified patients as having small duct PSC. Patients who did not undergo cholangiography and liver histology at the time of diagnosis were excluded from analysis. Co-occurrence of AIH was diagnosed in case of simultaneously increased levels of transaminases and immunoglobulin G, and/or the presence of autoantibodies (including antismooth muscle, antiliver cytosol, antiliver kidney microsome type 1, or antinuclear antibodies.[5] We excluded patients with a baseline GGT <50 U/L as well as patients with missing baseline GGT or GGT results at 1 year after diagnosis.

2.4 | Data collection

Baseline (i.e., at the time of diagnosis) and follow-up data were drawn from UMCG patient records. Baseline variables included patient demographics, age at PSC diagnosis, presence of associated immune diseases in the patient, presence and type of IBD, initial treatment after diagnosis, and signs and symptoms at first presentation. Immunological, hematological, and biochemical laboratory results at baseline were also entered, including levels of GGT, aspartate aminotransferase (AST), alanine aminotransferase, ALP, total bilirubin, and APRI (AST to Platelet Ratio Index). APRI was calculated using the following formula: APRI = [(AST/upper limit of the normal AST range) × 100]/Platelet Count. Date of diagnosis was determined by the date of imaging (MRCP or ERCP) or histology, whichever came first. We collected annual follow-up information of the patients from diagnosis until the age of 25 years, or until death or transplantation. Follow-up data included laboratory results, updates on radiology and histology, persistent and/or new signs and symptoms, and treatment changes. We excluded patients with missing laboratory data that were taken within 3 months of the date of diagnosis and the date of 1 year after diagnosis of PSC.

2.5 | Outcome of interest

The outcome of interest was the occurrence of one or more of the following clinical endpoints (a) portal hypertensive complications, (b) biliary complications, (c) hepatobiliary malignancy, (d) liver transplantation, or (e) death from liver disease.

2.6 | Definitions of clinical endpoints

Portal hypertension was considered diagnosed when ascites was present on imaging, when varices were seen during endoscopy, when splenomegaly was confirmed on abdominal ultrasound, when a full blood count showed indications for hypersplenism (thrombopenia, leucopenia, or both), when hepato-fugal flow was seen in the portal vein, or when signs of encephalopathy were detected. Encephalopathy was considered diagnosed based on neurological examination or upon initiation of treatment with rifaximin or lactulose.

Biliary complications included strictures that required either balloon dilatation or stenting, or acute bacterial cholangitis. Bacterial cholangitis was considered confirmed when liver test abnormalities co-occurred with fever, jaundice, or pain in right upper quadrant, or when a positive blood culture was reported. Hepatobiliary malignancies included cholangiocarcinoma, gallbladder carcinoma, hepatocellular carcinoma, and pancreatic cancer.

2.7 | Data analysis

Data analyses were performed using IBM SPSS Statistics version 23.0 for Windows. Patients were classified according to the change in GGT (≤25% or >25% decrease) in the first year after diagnosis. Fisher's exact test and the Mann–Whitney *U* test were used to compare baseline data between the two groups. All tests were two-sided and the level of significance used was $p < 0.05$. Kaplan–Meier analysis and log-rank testing were performed to assess the occurrence of adverse clinical endpoints over time. Time was defined as the moment of PSC diagnosis until appearance of the first clinical endpoint, until 5 years postdiagnosis or until the last known follow-up date if 5 years of follow-up had not been completed. Patients who did not reach the clinical endpoint and who did not complete a follow-up of 5 years were censored. For patients with an incomplete follow-up, we calculated the follow-up index (FUI) defined by the actual observed follow-up period divided by the aimed follow-up period. This value can range between near 0 and near 1. The higher the FUI, the closer the follow up was to the aimed follow-up time, which is 5 years in this case. We analyzed specificity, sensitivity, and the negative predictive value of GGT change and clinical outcomes, using the χ^2 test. Frequencies of medication use at baseline with their confidence intervals were also calculated for both GGT groups. The ULN for GGT was 50 U/L.

3 | RESULTS

3.1 | Demographics

We identified 72 patients from the histopathology database of the UMCG, of which we included 43 patients with positive findings for pediatric-onset PSC on histology or imaging. The median (interquartile range [IQR]) age at diagnosis was 15.2 years (14.3–16.9) in the group with ≤25% decrease of GGT and 12.1 years (10.4–15.0) in the other group. A total of 37 cases had concurrent IBD, with UC being the predominant phenotype ($n = 30$) (Table 1). IBD was significantly more frequent in the group with >25% decrease of GGT.

3.2 | PSC characterization at diagnosis

Large duct involvement was observed in 5 patients (71%) of the group with ≤25% decrease of GGT and in 20 patients (56%) of the group with >25% decrease. Three patients (42%) had features of AIH in the group with ≤25% decrease versus 10 (28%) in the group with >25% decrease, of which 2 (66%) and 9 (90%) had positive autoantibodies, respectively. The remaining two were deemed to have AIH features based on characteristic histological findings in combination with elevated IgG levels.

3.3 | Clinical endpoints in the first 5 years after diagnosis

The median FUI (IQR) was 0.54 (0.37–0.70), with 28 of 43 patients (65%) who had completed a follow-up of 5 years. Nine of 43 patients

TABLE 1 Patient characteristics at diagnosis of pediatric-onset PSC.

	GGT decreased ≤ 25% from diagnosis (n = 7)	GGT decreased > 25% from diagnosis (n = 36)	p Value
Demographics			
Median age at diagnosis in years (IQR)	15.2 [14.3–16.9]	12.1 [10.4–15.0]	0.078
Male gender, n (%)	5 (71%)	22 (61%)	0.70
Ethnicity			
Caucasian, n (%)	6 (86%)	34 (94%)	0.18
African, n (%)	0 (0%)	2 (6%)	
Unknown, n (%)	1 (14%)	0 (0%)	
PSC in first-degree family member, n (%)	0 (0%)	2 (6%)	0.31
Associated (autoimmune) disease[a]	0 (0%)	3 (8%)	0.68
Liver-related symptoms at diagnosis			
Fatigue, n (%)	4 (57%)	15 (42%)	0.68
Hepatomegaly, n (%)	5 (71%)	8 (22%)	0.13
Splenomegaly, n (%)	3 (43%)	7 (19%)	0.64
Pruritis, n (%)	0 (0%)	6 (17%)	0.57
Jaundice n (%)	1 (14%)	4 (11%)	>0.99
PSC characteristics			
Large duct involvement, n (%)	5 (71%)	20 (56%)	0.73
Features of autoimmune hepatitis, n (%)	3 (42%)	10 (28%)	0.66
ANA positive, (n)	2	10	>0.99
anti-LKM-1 positive, (n)	0	0	
anti-SMA positive, (n)	1	11	>0.99
anti-LC-1 positive, (n)	0	0	
IBD characteristics			
Concurrent IBD, n (%)	3 (43%)	34 (94%)	0.04
IBD phenotype			
Ulcerative colitis, n (%)	3 (100%)	27 (75%)	>0.99
Crohn's disease, n (%)	0 (0%)	3 (8%)	
IBD-unclassified, n (%)	0 (0%)	4 (11%)	
Timing of IBD diagnosis			
Simultaneous with PSC diagnosis, n (%)	1 (14%)	20 (56%)	0.33
After PSC diagnosis, n (%)	1 (14%)	3 (8%)	
Before PSC diagnosis, n (%)	1 (14%)	11 (31%)	

Note: Fisher's exact test was used for categorical variables. Mann–Whitney U test was used for not normal distributed continuous variables.

Abbreviations: ANA, antinuclear antibodies; GGT, gamma-glutamyl transferase; IBD, inflammatory bowel disease; IQR, interquartile range; LC-1, liver cytosol; LKM-1, liver kidney microsome type 1; PSC, primary sclerosing cholangitis; SMA, smooth muscle antibodies.

[a]Arthralgias, diabetes mellitus, autoimmune thyroiditis, celiac disease, or thrombocytopenia.

(21%) had developed portal hypertensive or biliary complications within 5 years of diagnosis as a first event, of which two had undergone a liver transplantation.

All patients had increased GGT levels at diagnosis (>50 U/L). Figure 1 shows that among 36 patients with a decrease of GGT of at least 25% within 1 year of diagnosis, the probability of developing one or more complications in the first 5 years after diagnosis was 20%, compared to 50% in patients without a decrease of GGT of at least 25% (p = 0.031). Hepatobiliary malignancies or death did not occur in the time frame of our study. Liver transplantation did not

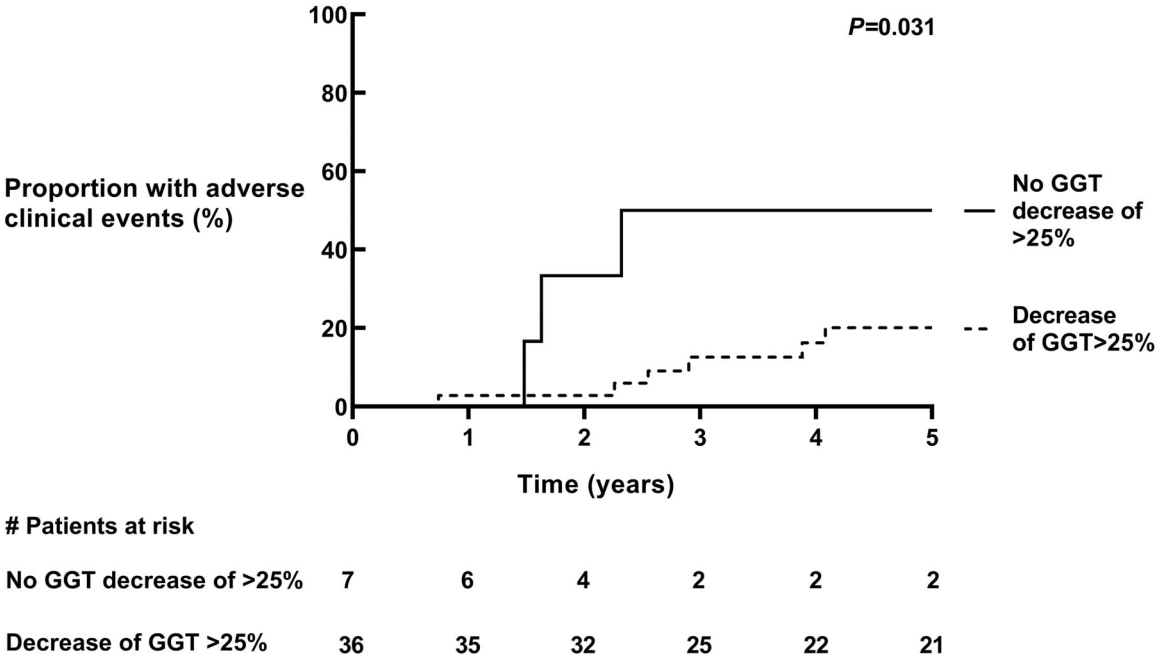

FIGURE 1 Relationship between GGT reduction in the first year after diagnosis of PSC and event-free survival in the first 5 years after diagnosis. Event is defined as development of portal hypertensive complications, biliary complications, hepatobiliary malignancy, liver transplantation, or death. Time is defined as time from diagnosis until the first event or 5 years after diagnosis. GGT, gamma-glutamyl transferase; PSC, primary sclerosing cholangitis.

occur as a single event but was preceded by biliary or portal hypertensive complications.

Fewer patients with PSC-IBD had adverse clinical events than patients with isolated PSC (Fisher's exact, $p = 0.04$, Table 1). We observed no significant differences in event-free survival between PSC versus PSC with features of AIH (log-rank, $p = 0.37$, data not shown). The sensitivity was 33%, the specificity was 88.2%, and the negative predictive value of GGT was 83%.

3.4 | GGT change

Median baseline GGT (IQR) was not statistically different between groups: 236 (120–454) in the group of ≤25% decrease and 413 (198–508) in the other group. At 1 year, median GGT increased up to 8 times the ULN in the group of ≤25% decrease, while in the other group the median level normalized. Absolute GGT levels at diagnosis were not associated with the percentage change in 1 year (data not shown). Six of seven patients with a GGT decrease <25% actually showed an *increase* in the first year after diagnosis.

All patients were treated from baseline onwards with at least one of the following drugs: ursodeoxycholic acid (UDCA), prednisone, thiopurines, or mesalamine. Figure 2 shows that 7 of 43 patients (16%, confidence interval [CI] 8%–30%) had lack of GGT normalization 1 year after baseline. Among those treated with UDCA, prednisone, azathioprine, or mesalamine, the proportion without GGT normalization was 11%, 14%, 14%, and 7%, respectively. Thus, whether or not there was normalization of GGT 1 year postdiagnosis was irrespective of the medication prescribed at baseline.

4 | DISCUSSION

In this single-center cohort study, we show that absence of a decrease of at least 25% of GGT within the first year after diagnosing pediatric-onset PSC is strongly associated with early occurrence of adverse clinical events. This finding is in accordance with the observations done in an international pediatric retrospective cohort described by Deneau et al.[3,13] They concluded that a normalized GGT (<50 U/L), a percentage decrease of >25%, or both at 1 year after PSC diagnosis was associated with lower rates of long-term adverse outcomes and predicted a favorable clinical outcome.[3] We found no significant differences in event-free survival between patients with PSC and patients with overlap syndrome, which is in line with the observations of Deneau et al.[3,14] The co-occurrence of IBD, on the other hand, was associated with more favorable outcomes than isolated PSC. This association has also been described in the large international multicenter cohort by Deneau et al.[14]

We found no proof that the use of prednisone or azathioprine, as a proxy for the PSC sub-phenotype with features of AIH, led to improved GGT levels 1-year postdiagnosis. The earlier mentioned study by Deneau et al., as well as a large study among adults have also shown that patients with the PSC sub-phenotype with autoimmune features do not have a milder disease course.[3,15]

Our study underwrites the robustness of GGT change as a predictor of disease progression. Identifying pediatric patients who

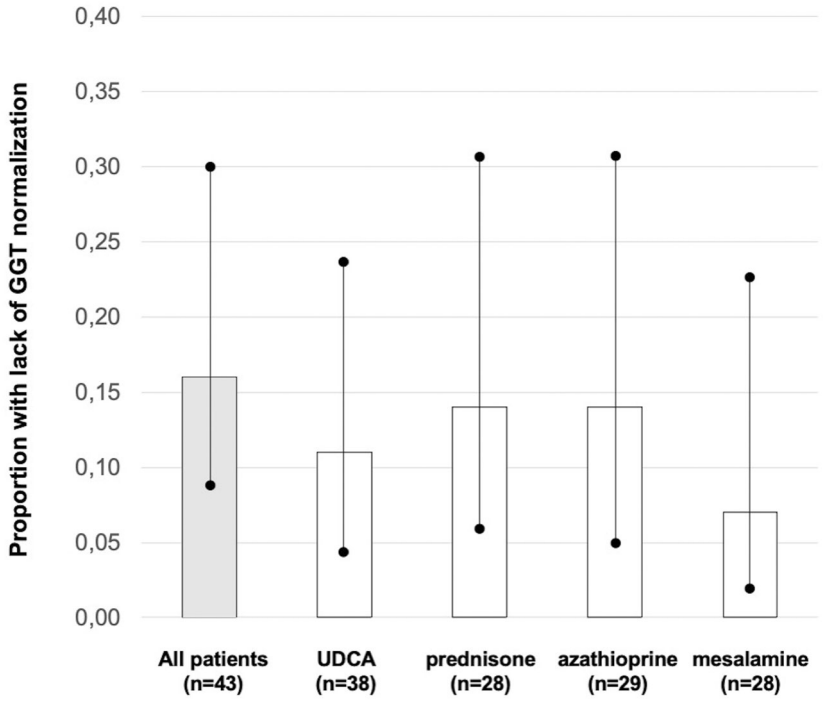

FIGURE 2 Proportion of patients with lack of GGT normalization 1-year postdiagnosis according to medication prescribed at baseline. Whiskers indicate 95% confidence intervals. GGT, gamma-glutamyl transferase; UDCA, ursodeoxycholic acid.

have a high likelihood of disease progression within 5 years from diagnosis allows early counseling, close monitoring for potential severe complications, and timely referral to a liver transplantation center. Potential drawbacks of our study relate to its retrospective nature and the limited sample size. Another limitation is that not every patient had already completed the 5-year follow-up. Accordingly, the ("true") occurrence and frequency of hepatic complications in pediatric-onset PSC could therefore be even higher than reported here. The use of a clear methodology for assessment of the diagnosis and the meticulous documentation of clinical follow-up data should be considered a strength and will lay the foundation for future registry-based research initiatives on PSC.

In conclusion, our data provide insights into the course of disease in pediatric-onset PSC. A GGT decrease >25% within 1 year of diagnosis is a predictor of a relative benign disease course in the first 5 years postdiagnosis. This provides physicians, patients, and parents with clearer insights into the course and prognosis of PSC and may help in assessing the efficacy of future therapeutics. Healthcare professionals who treat patients with pediatric-onset PSC are advised to monitor them closely to recognize complications early and control long-term sequelae. Finally, our study emphasizes the importance of long-term follow-up of pediatric patients with rare diseases across the age of transfer to adult-oriented care, as otherwise pediatricians may tend toward giving a too rosy view of the disease course.

AUTHOR CONTRIBUTIONS

Besrat Berhane: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; validation; visualization; writing – original draft; writing – review and editing. **Patrick F. van Rheenen**: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; supervision; validation; visualization; writing – original draft; writing – review and editing. **Henkjan J. Verkade**: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; supervision; validation; visualization; writing – original draft; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

TRANSPARENCY STATEMENT

The lead author Henkjan J. Verkade affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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How to cite this article: Berhane B, van Rheenen PF, Verkade HJ. Gamma-glutamyl transferase and disease course in pediatric-onset primary sclerosing cholangitis: a single-center cohort study. *Health Sci Rep*. 2023;6:e1086. doi:10.1002/hsr2.1086