Evidence-Based Case Report

# The Predictive Value of Gamma-Glutamyl Transferase on Jaundice Clearance in Biliary Atresia: An Evidence-Based Case Report and Meta-Analysis

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**Abstract:**

***Background:*** Biliary atresia (BA) is a neonatal condition characterized by the obstruction of extrahepatic bile ducts.

***Case:*** A 2-year-old female with BA underwent a Kasai procedure at 3 months of age. Despite the surgery, she developed persistent jaundice and abdominal enlargement. Preoperative laboratory findings revealed elevated liver enzymes, GGT, and bilirubin levels. This case raises the clinical question of whether preoperative GGT levels can predict JC after the Kasai procedure, in addition to its role in diagnosis.

***Methods:*** A systematic literature search was performed on 4 databases (PubMed, Scopus, Cochrane, and Proquest) by using relevant keywords and identified seven high quality studies.

***Results:*** Five studies found higher GGT levels in patients who achieved JC following Kasai surgery, compared to those with unsuccessful jaundice clearance (JUC). However, two studies reported conflicting findings. A pooled analysis indicated a non-significant trend toward higher GGT levels in the JC group compared to the JUC group (WMD: 65.6, 95% CI: -58.6; 189.8).

***Conclusion:*** Elevated preoperative GGT levels may be associated with improved JC in BA patients. However, further investigation to validate these findings, determine the optimal role of GGT in assessing prognosis, and later, guiding treatment decisions in BA patients.

**Keywords:** biliary atresia, gamma-glutamyl transferase, jaundice clearance, kasai surgery, prognosis

## Introduction

Biliary atresia (BA) is a neonatal disease characterized by the obstruction of extrahepatic bile ducts.[1] Most infants with BA present with pale stool and elevated levels of Gamma-Glutamyl Transferase (GGT), AST, ALT, and direct bilirubin. Abdominal ultrasound and liver histopathology can support the diagnosis.[2] The Kasai procedure is the primary treatment for BA. Successful Kasai surgery can improve bilirubin drainage and enable long-term native liver survival.[3] Most infants undergoing the Kasai procedure before 60 days of age will achieve jaundice clearance (JC).[2] Infants who experience JC after surgery are expected to have long-term survival with their native liver. Numerous studies have analyzed the prognostic factors for infants with BA who underwent the Kasai procedure and achieved JC, focusing on both preoperative and postoperative variables.[1, 4]

This study aims to investigate the prognostic significance of preoperative GGT levels in infants undergoing the Kasai procedure, in addition to its role as a diagnostic marker.

## Case Illustrations

A 2-year-and-4-month-old female toddler was referred to Cipto Mangunkusumo Hospital from a private hospital after a one-month hospitalization. The initial reason for admission to the first hospital was a four-day history of vomiting (eight episodes). The patient also experienced fever (38°C) and black, bloody stools during this hospitalization. The patient's mother reported several infections, including gastric, intestinal, and respiratory infections.

The patient had been diagnosed with biliary atresia 1.5 months after birth and underwent the Kasai procedure at 3 months of age. The initial complaint was jaundice, noticeable in bright light, at 30 days of age. The patient had acholic stools from birth, and ultrasound findings were suggestive of biliary atresia. Following the Kasai procedure, the patient's jaundice was persistent, and her abdomen gradually enlarged. There was no history of meconium stools before or after the surgery. The patient was underweight, severely stunted, and severely wasted with hepatomegaly, splenomegaly, and a yellowish-green skin hue with decreased subcutaneous fat. The patient was diagnosed with cholangitis, post-Kasai procedure biliary atresia, and malnutrition.

Preoperative laboratory investigations revealed elevated liver enzymes (AST 226 U/L, ALT 111 U/L), increased gamma-glutamyl transferase (GGT) level (257 U/L), increased alkaline phosphatase (692 U/L), and hyperbilirubinemia (total 20.54 mg/dL, direct 14.15 mg/dL, indirect 6.39 mg/dL).

The diagnosis of biliary atresia was based on three findings: acholic stools, significantly elevated GGT levels (above 250 U/L), and ultrasound findings suggestive of biliary atresia. Subsequently, clinicians inquired whether the elevated preoperative GGT levels in this patient could potentially predict jaundice clearance after the Kasai procedure, in addition to its diagnostic role. Motivated by this clinician query, this case report contributes to the exploration of GGT as a potential prognostic factor in this patient population.

## Clinical Question

Therefore, an evidence-based case report was conducted with the clinical question: "Can preoperative GGT levels predict jaundice clearance following Kasai surgery in infants with biliary atresia?". This clinical question was broken down into the PICO format:

- Patient: Infants with biliary atresia who underwent Kasai surgery
- Intervention: Preoperative GGT levels
- Comparison: -
- Outcome: Jaundice clearance

## Methods

### Data Sources and Search Strategy

A comprehensive literature search was conducted in four electronic databases: Scopus, PubMed, Cochrane Library, and ProQuest. The search strategy utilized a combination of keywords, including "jaundice clearance," "gamma-glutamyl transferase," and "biliary atresia." These terms were searched as both free text and, where applicable, Medical Subject Headings (MeSH) terms. Boolean operators (AND, OR) were used to refine the search results. The search queries for each database can be found in **Table 1**. Additionally, the references of included studies were screened manually to identify any further relevant studies through the hand-searching process. All studies were then compiled into a spreadsheet for further screening.

Table 1. Search queries and first-hit results of each electronic database.

| Database | Keyword | First-hit articles |
|---|---|---|
| SCOPUS | ( "jaundice-free" OR "jaundice clearance" OR outcome ) AND ( "gamma-glutamyl transpeptidase" OR "gamma glutamyl transpeptidase" OR "gamma-glutamyl transferase" OR "gamma glutamyl transferase" ) AND "biliary atresia" | 551 |

| | | |
|---|---|---|
| PUBMED | (biliary atresia[MeSH Terms]) AND (gamma glutamyl transpeptidase[MeSH Terms]) AND ("jaundice-free" OR "jaundice clearance" OR "liver survival") | 4 |
| COCHRANE | ("jaundice-free" OR "jaundice clearance" OR outcome) AND Gamma-Glutamyltransferase | 5 |
| PROQUEST | ("jaundice clearance" OR outcome) AND "gamma glutamyl transferase") AND "biliary atresia" | 12 |

**Article Screening Process**

All authors conducted the screening process independently to ensure objective assessment during the screening stage. Studies were included if they met the following criteria: (1) Original research articles assessing the role of GGT in predicting jaundice resolution in patients with biliary atresia; (2) Studies involving pediatric patients diagnosed with biliary atresia; (3) Studies that reported jaundice clearance as an outcome; (4) Articles published in English.

Meanwhile, we excluded case reports, review articles, conference abstracts, and articles that did not report specific data on GGT levels or jaundice resolution. Studies with a high risk of bias, as assessed by the Oxford Centre for Evidence-Based Medicine (CEBM) prognosis critical appraisal tool after the initial screening process, were also excluded. Articles with different screening outcomes by each author were discussed further within a group discussion.

**Data Extraction**

Data extraction was conducted independently by four reviewers using a standardized data extraction form in a spreadsheet. The extracted data included study characteristics (authors, year of publication, country), patient demographics (age, gender), study design, sample size, GGT levels, jaundice clearance outcomes, and the duration of follow-up. We also extracted the results of bivariate analysis used in the articles to determine the effect of GGT level on jaundice clearance outcome, if available. Any discrepancies were resolved through discussion or by consulting with others if necessary.

**Data Synthesis**

A meta-analysis was conducted to synthesize the results of the included studies with similar outcomes. This statistical technique will allow for a quantitative summary of the overall effect size and identify any heterogeneity among these studies. We conduct a random-effect continuous meta-analysis using mean difference as effect size. The results will be extrapolated into forest plots.

**Quality Assessment**

The quality of the included studies was assessed using the Oxford Centre for Evidence-Based Medicine (CEBM) prognosis critical appraisal tool. This tool evaluates studies based on criteria such as patient selection, prognostic factor measurement, outcome measurement, and statistical analysis. Studies were classified as high, moderate, or low quality based on their scores. The quality assessment was conducted independently by all reviewers, with discrepancies resolved through group discussion.

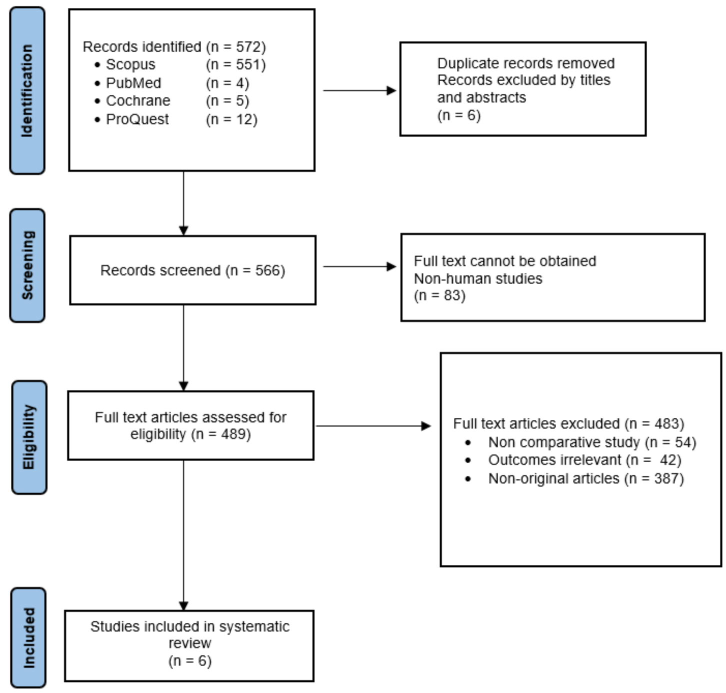


Figure 1. PRISMA flowchart on study screening and selection process.

**Ethical Considerations**

As this study involved a systematic literature review, ethical approval was not required. All data used in this review were derived from publicly available sources.

# Results

Seven retrospective cohort studies were included in this analysis, with a summary of the included studies presented in **Table 2**. The critical appraisal result of each study is presented in **Table 3**. The studies by Sun et al.[5] and Shankar et al.[6] were the only ones that used a cut-off value for GGT levels. Sun et al. used 300 IU/L as the GGT cut-off value to divide the participants into low and high-level groups. The high-level group had a higher rate of jaundice clearance (JC) compared to the low-level group.[5] Meanwhile, Shankar et al. divided patients into two groups: <200 IU/L (normal) and

≥200 IU/L (high). Half of the patients (51%) in the high-level group achieved JC, compared to only 36% in the low-level group, although this difference was not statistically significant (P = 0.39).[6]

Zhang et al.[4] divided their cohort into training and testing groups, which were further divided into jaundice clearance (CJ) and unsuccessful jaundice clearance (UJC) groups. Zhang et al.[4] divided their cohort into training and testing groups, which were further divided into jaundice clearance (CJ) and unsuccessful jaundice clearance (UJC) groups. This study transformed the GGT value into logarithm. Both groups showed that patients who achieved CJ had higher GGT levels (6.3±0.8, 6.2±0.6) than those in the UJC group (5.7±0.8, 5.8±0.6), with these differences being statistically significant (P < 0.001).[4] A two-year follow-up study by Yassin et al.[1] showed that preoperative GGT levels in patients with JC 6 months postoperatively had a higher median value (846.5 vs. 802), although the difference was not statistically significant (P = 0.45).[1]

Qi et al.[3] analyzed 151 biliary atresia patients who underwent the Kasai procedure. One hundred and one patients achieved JC, with 67 achieving JC within three months and 34 achieving JC between three and six months. The mean GGT level in the JC group was 675 ± 473, while in the JUC group, it was 606 ± 443.[3]

Abdel-Aziz et al.[7] and Ihn et al.[8] reported results that contradicted other studies. In both studies, lower preoperative GGT levels were good predictors of surgical outcome, which was the clearance of jaundice. In Abdel-Aziz et al., a GGT level of 491 U/L or less was predictive of a successful outcome, and higher GGT levels were significantly associated with unsuccessful jaundice clearance (UJC) (P = 0.041).[7] In the study by Ihn et al., the GGT level in JC patients was 451.3, while in the JUC group, it was 499.9 (P = 0.429).[8]

Outcome assessment was conducted on three studies with similar outcome types, consisting of a statistical meta-analysis. The pooled analysis indicated a non-significant trend towards higher GGT levels in the JC group compared to the JUC group (WMD: 65.6, 95% CI: -58.6; 189.8) (**Figure 2**).

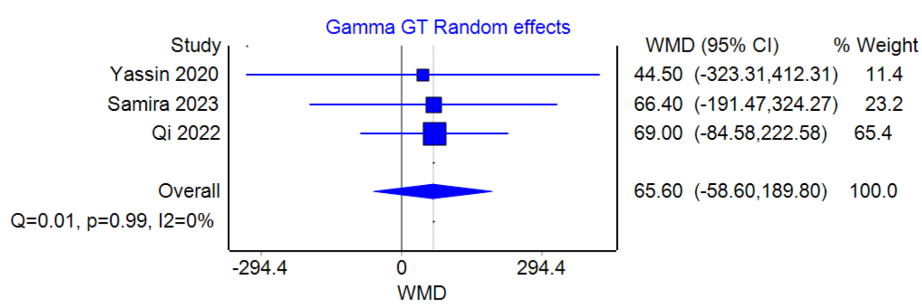


Figure 2. Pooled analysis of mean GGT level.

Table 2. Characteristics of included studies.

| Author, year | Study Design | Study Location | Sample number | Age at Procedure | Pre-operative GGT Values | Number JC and JUC patients | LoE* |
|---|---|---|---|---|---|---|---|
| Ihn K et al., 2018[8] | Restrospective cohort | Seoul, Korea | 169 | 63.7 ± 31.8 days | JC: 451.3 ± 341.1 IU/L<br>JUC: 499.9 ± 373.2 IU/L | JC: 125<br>JUC: 44 | 2b |
| Shankar S et al., 2020[6] | Restrospective cohort | Victoria, Australia | 113 | 61 days (30 – 149 days) | Low GGT: <200 IU/L<br>High GGT: ≥200 IU/L | JC Low: 5 High: 50<br>JUC Low: 9 High: 44 | 2b |
| Yassin A et al., 2020[1] | Restrospective cohort | Cairo, Egypt | 75 | 82 ± 23 days | JC group: 419 (503) IU/L<br>JUC group: 414 (646) IU/L | JC: 28<br>JUC: 47 | 2b |
| Sun S et al., 2022[5] | Restrospective cohort | Shanghai, China | 1998 | Low GGT group: 64.71 ± 21.35 days<br>High GGT group: 68.64 ± 22.42 days | Low GGT group: ≤300 IU/L<br>High GGT group: >300 IU/L | Low GGT: 167<br>High GGT: 730 | 2b |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Qi Q et al., 2022[3] | Restro-spective cohort | Shenyang, China | 151 | JC group: 58 (18 days)<br>JUC group: 68 (20 days) | JC group: 675 (473) IU/L<br>JUC group: 606 (443) IU/L | JC: 101<br>JUC: 50 | 2b |
| Zhang Y et al., 2022[4] | Restro-spective cohort | Chengdu, China | 175 | Training group:<br>CJ: 61.2 ± 20.0 days<br>UJ: 68.2 ± 19.3 days<br>Testing group:<br>CJ: 63.81 ± 18.9 days<br>UJ: 69.8 ± 19.2 days | Training group:<br>CJ: ln 6.3 ± 0.8 IU/L<br>UJ: ln 5.7 ± 0.8 IU/L<br>Testing group:<br>CJ: ln 6.2 ± 0.6 IU/L<br>UJ: ln 5.8 ± 0.6 IU/L | Training group:<br>JC: 83<br>JUC: 37<br>Testing group:<br>JC: 37<br>JUC: 18 | 2b |
| Abdel-Aziz SA et al., 2023[7] | Restros pective cohort | Menoufia, Egypt | 100 | JC group: 68.8 ± 14.8 days<br>JUC group: 80.9 ± 184.7 days | JC: 965.1 ± 666.8 IU/L<br>JUC: 898.7 ± 507 IU/L | JC: 33<br>JUC: 67 | 2b |

Data presented as mean ± standard deviation or median (interquartile range).
*LoE: Level of evidence, for prognostic studies were determined using the Cochrane classification.

Table 3. Critical appraisal of included studies.

| Author, year | | Ihn K et al., 2018[8] | Shankar S et al., 2020[9] | Yassin A et al., 2020[1] | Sun S et al., 2022[5] | Qi Q et al., 2022[3] | Zhang Y et al., 2022[4] | Abdel-Aziz et al., 2023[7] |
|---|---|---|---|---|---|---|---|---|
| Validity | Representative sample of patients | + | + | + | + | + | + | + |
| | Follow-up sufficient | + | + | + | + | + | + | + |
| | Objective/ blind outcome | + | + | + | + | + | + | + |
| | Adjustment for prognostic factors | + | + | + | + | + | + | + |
| Importance | Odds ratio | N/A | 0.54 | N/A | 0.52 | N/A | 0.41 | N/A |
| | Prognostic estimates (95% CI) | N/A | 0.17 – 1.74 | N/A | 0.41 – 0.65 | N/A | 0.22 – 0.80 | 0.51 – 0.74 |
| Applicability | Similarity to the patient on the case | + | + | + | + | + | + | + |
| | Clinically importance on conclusion | + | + | - | + | - | + | + |

N/A: Not available

## Discussion

Studies have shown that rapid and complete jaundice clearance (JC) following the Kasai procedure (KP) is a crucial indicator of long-term native liver survival.[4, 8] While previous research has identified certain clinical factors associated with unsuccessful JC, accurately predicting JC at early stage remains challenging in clinical practice.[8] A timely and precise prediction of JC is essential for clinicians to assess risk stratification, estimate prognosis, develop individualized treatment plans, and prepare for potential liver transplantation.[4]

Gamma-glutamyl transferase (GGT) is primarily found in the hepatobiliary system, kidneys, spleen, seminal vesicles, and brain. However, the main sources of GGT are hepatocytes and biliary epithelial cells.[10] Elevated GGT levels (>300 IU/L) have been shown to accurately differentiate biliary atresia (BA) from neonatal hepatitis (NH) with 85% accuracy.[11] The study by Shen et al.[12] also found that infants with cholestasis and higher GGT levels were more likely to be diagnosed with BA. While GGT activity is often overlooked as a routine laboratory test in BA patients, its prognostic role remains relatively unexplored. Unlike its diagnostic utility, the longitudinal trends of serum GGT levels following the Kasai procedure (KP) have not been extensively studied.[8]

Our analysis of existing studies reveals that in five out of seven studies, patients with higher preoperative GGT levels were more likely to achieve jaundice clearance within six months than those with lower levels. This finding aligns with the known role of GGT in humans. GGT facilitates the transfer of the glutamyl group from glutathione, which helps replenish intracellular glutathione levels and supports bile-acid independent bile flow. A GGT deficiency could potentially exacerbate oxidative stress damage in the liver.[13]

However, the studies by Abdel-Aziz et al.[7] and Ihn et al.[8] found that lower preoperative GGT levels were more beneficial than higher levels for postoperative outcomes in BA patients. In BA patients, liver pathology worsens with age, accompanied by an increase in proliferation and a corresponding rise in GGT levels.[11] This may explain the results of both studies, as the patients who failed to achieve JC underwent the procedure at an older age (JC: 68.8±14.8 vs UJC: 80.9±184.7), while the other studies had similar procedure times for both patients who achieved JC and those who did not. Furthermore, our meta-analysis did not provide sufficient evidence to conclude that GGT levels were significantly higher in the JC group compared to the JUC group (WMD: 65.6, 95% CI: -58.6; 189.8) (**Figure 2**). Given the wide confidence interval and non-significant p-value, the clinical implications of this finding are uncertain.

Even though the available evidence is not entirely consistent, our findings suggest that GGT levels may have some prognostic value in predicting jaundice clearance (JC) in biliary atresia (BA) patients undergoing the Kasai procedure. Therefore, GGT could be incorporated into patient management and counseling by providing valuable information for risk stratification, prognosis estimation, and treatment planning.[14]

We acknowledge that our study has limitations, including its retrospective nature, single-center design, and small sample size, which may introduce bias. Therefore, further research is needed to establish definitive guidelines for the use of GGT in BA patients. By conducting larger studies and validating the findings, GGT could become a valuable tool for clinicians in assessing the prognosis of BA patients and guiding their treatment decisions.

## Conclusion

Our findings suggest that elevated preoperative GGT levels may be associated with improved JC in BA patients. However, further investigation to validate these findings, determine the optimal role of GGT in assessing prognosis, and later, guiding treatment decisions in BA patients.

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## Funding Statement

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## Conflict of Interest

None declared.

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