Semiquantitative Histomorphological Grading Of Tissue MMP-7 Immunohistochemical Expression In Pediatric Biliary Atresia: A Clinicopathological Study

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Introduction

Liver biopsy remains fundamental in the evaluation of neonatal cholestasis. Characteristic histopathological features, including bile duct proliferation, bile plugs, portal stromal oedema, ductular reaction, and portal fibrosis, offer important diagnostic clues for biliary atresia (BA) [1].

Preoperative liver biopsy demonstrates high accuracy in distinguishing BA from other causes of neonatal cholestasis and guides surgical management [2].

Biliary atresia is a progressive fibro-obliterative cholangiopathy of infancy. In the absence of treatment, it represents the leading indication for paediatric liver transplantation [3].

Despite significant advances in understanding the disease, the precise aetiology of BA remains unclear. Current evidence indicates contributions from genetic, developmental, immune-mediated, and environmental factors [4].

Early recognition and prompt Kasai portoenterostomy are essential for native liver survival and improved long-term outcomes [5].

Recent reviews have further highlighted the multifactorial pathogenesis of BA and the persistent need for reliable diagnostic biomarkers to complement conventional histopathological assessment [6–8].

Although imaging modalities have enhanced the evaluation of neonatal cholestasis, histopathological examination of liver biopsy specimens remains a crucial component of the diagnostic work-up [9].

Intraoperative cholangiography provides definitive confirmation of BA but is invasive and reserved for infants with strong clinical suspicion [10].

Proteomic studies have identified matrix metalloproteinase-7 (MMP-7) as significantly upregulated in infants with BA, indicating a potential role in biliary epithelial injury and disease pathogenesis [11].

Studies demonstrate increased hepatic MMP-7 expression in the biliary epithelium, indicating that MMP-7 immunohistochemistry may yield information beyond routine histomorphology [12].

However, there are few studies describing the histomorphological spectrum and semiquantitative grading of tissue MMP-7 immunohistochemical expression in paediatric biliary atresia.

Therefore, this study aims to characterize the histomorphological spectrum of tissue MMP-7 immunohistochemical expression in paediatric biliary atresia using a semiquantitative grading system and representative histopathological features.

Objectives

1. Describe the distribution of MMP-7 immunohistochemical grades (1–5).
2. Characterize staining intensity and localization patterns.
3. Correlate staining grade with expression category (high/low).
4. Illustrate the histological spectrum using representative photomicrographs.
5. Describe associated H&E findings, including giant cell transformation where present.

MATERIALS AND METHODS

Study Design

This retrospective observational study was conducted to evaluate the histomorphological spectrum and semiquantitative grading of tissue matrix metalloproteinase-7 (MMP-7) immunohistochemical expression in pediatric biliary atresia.

Study Setting
The study was conducted in the Department of Pathology, Sree Balaji Medical College and Hospital, Bharath Institute of Higher Education and Research (BIHER), Chennai, using archived liver biopsy specimens received from Dr. Rela Institute and Medical Centre, Chennai.

Study Period
Archived liver biopsy specimens collected between January 2020 and December 2024 were included. Histopathological review, immunohistochemical evaluation, data analysis, and manuscript preparation were carried out during 2025–2026.

Study Population
The study included 38 pediatric patients with histopathologically confirmed biliary atresia. Archived formalin-fixed paraffin-embedded liver biopsy specimens from these patients were retrieved and evaluated for tissue MMP-7 immunohistochemical expression.

Inclusion Criteria
- Archived formalin-fixed paraffin-embedded liver biopsy specimens with a confirmed diagnosis of biliary atresia.
- Adequate tissue for histopathological review and MMP-7 immunohistochemistry.
- Infants and children younger than 18 years.

Exclusion Criteria
- Inadequate or non-representative biopsy specimens.
- Poorly fixed or poorly processed tissue.
- Specimens showing extensive necrosis or hemorrhage.
- Cases with incomplete histopathological records.

Histopathological Evaluation
Archived hematoxylin and eosin-stained sections were reviewed by experienced pathologists. Histopathological evaluation included assessment of bile duct proliferation, ductular reaction, portal inflammation, cholestasis, giant cell transformation, and other routine microscopic features of biliary atresia.

Immunohistochemistry
Four-micrometre-thick sections were prepared from formalin-fixed paraffin-embedded tissue blocks and mounted on poly-L-lysine-coated slides. Following deparaffinization, antigen retrieval was performed using citrate buffer in a microwave oven. Endogenous peroxidase activity was blocked using 3% hydrogen peroxide. Sections were incubated with anti-MMP-7 primary antibody (1:100 dilution) for one hour at room temperature. Immunoreactivity was detected using a horseradish peroxidase polymer detection system with 3,3'-diaminobenzidine (DAB) as the chromogen and counterstained with Gill's hematoxylin. Positive control sections recommended by the manufacturer were included in each staining run, while negative controls were prepared by omission of the primary antibody.

Evaluation of MMP-7 Immunohistochemical Expression
Tissue MMP-7 expression was evaluated using a semiquantitative grading system based on staining intensity and distribution.
- **Grade 1:** No staining
- **Grade 2:** Apical or luminal staining with low intensity
- **Grade 3:** Complete epithelial staining with weak intensity
- **Grade 4:** Moderate epithelial staining with periportal hepatocyte involvement
- **Grade 5:** Strong diffuse biliary epithelial staining

For descriptive analysis, MMP-7 expression was categorized as low expression (Grades 1–3) and high expression (Grades 4–5). Histomorphological staining patterns, including diffuse, apical, focal, mixed, and dot-like staining, were also documented.

Outcome Measures
The primary outcome was to describe the semiquantitative grading and histomorphological spectrum of tissue MMP-7 immunohistochemical expression in pediatric biliary atresia.

Statistical Analysis
Data were analyzed using IBM SPSS Statistics (Version XX; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (interquartile range), while categorical variables were summarized as frequencies and percentages. Descriptive statistics were used to evaluate the distribution of MMP-7 grades, expression categories, and staining patterns. Associations between categorical variables were assessed using the Chi-square test or Fisher's exact test, where appropriate. A p-value of <0.05 was considered statistically significant.

Results

Clinical Characteristics
The study included 38 pediatric patients with histopathologically confirmed biliary atresia. Of these, 20 were female (52.6%) and 18 were male (47.4%). Most patients presented within the first three months of life. MMP-7 immunohistochemistry was completed for all biopsy specimens; however, the amount of tissue available for assessment was limited in one case.
The clinical characteristics of the study population are presented in Table 1.

Table 1. Clinical characteristics of the study population (n = 38)

Variable	Value
Number of cases	38
Male	18 (47.4%)
Female	20 (52.6%)
Mean MMP-7 grade	3.78
Median MMP-7 grade	4

Distribution of MMP-7 Immunohistochemical Grades
MMP-7 staining ranged from Grade 2 to Grade 5. Grade 5 was the most common score, recorded in 10 cases (26.3%), followed by Grade 3 in 9 cases (23.7%) and Grade 4 in 8 cases (21.1%). Half-step scores of 2.5, 3.5, and 4.5 occurred less often and reflected intermediate levels of staining within the semiquantitative scale.
The mean MMP-7 grade was 3.78, and the median grade was 4.
The frequency of each MMP-7 grade is shown in Table 2.

Table 2. Distribution of MMP-7 immunohistochemical grades

Grade	Number (%)
Grade 2	3 (7.9)
Grade 2.5	1 (2.6)

Grade 3	9 (23.7)
Grade 3.5	1 (2.6)
Grade 4	8 (21.1)
Grade 4.5	3 (7.9)
Grade 5	10 (26.3)
Total	38 (100)

MMP-7 Expression Profile

According to the predefined semiquantitative criteria, high MMP-7 expression was identified in 20 cases (52.6%), while low expression was observed in 18 cases (47.4%).

Grades 4 and 5 occurred mainly in the high-expression group, whereas Grades 2 and 3 were more often seen in cases classified as having low expression.

Table 3 presents the distribution of the high- and low-expression categories.

Table 3. MMP-7 expression profile

Expression	Number (%)
High	20 (52.6)
Low	18 (47.4)

Histomorphological Patterns of MMP-7 Immunoexpression

MMP-7 immunoreactivity showed several histomorphological patterns. Moderate cytoplasmic staining was the most frequent pattern, occurring in 17 cases (44.7%). Strong staining was observed in 10 cases (26.3%), and weak staining was present in 5 cases (13.2%).

Less common patterns comprised apical staining in 3 cases (7.9%) and mixed, focal, and dot-like staining in 1 case each (2.6%).

Thus, although all patients shared the same diagnosis, the tissue distribution and intensity of MMP-7 staining were not uniform.

Table 4 lists the observed staining patterns and their frequencies.

Table 4. Histomorphological staining patterns

Pattern	Number (%)
Moderate	17 (44.7)
Strong	10 (26.3)
Weak	5 (13.2)
Apical	3 (7.9)
Mixed	1 (2.6)

Focal	1 (2.6)
Dot-like	1 (2.6)

Association Between MMP-7 Grade and Histomorphological Pattern

Staining morphology differed across the semiquantitative grades. Weak immunoreactivity was concentrated in the lower grades, moderate cytoplasmic staining was most evident at intermediate grades, and strong immunoreactivity became more frequent at higher grades. Some variation within individual grades was nevertheless observed.

Apical staining occurred in a few intermediate- and high-grade cases. Focal and dot-like patterns were each limited to a single case, and one biopsy showed a mixed staining pattern.

Taken together, the findings indicate a shift from weak to more intense immunoreactivity as the MMP-7 grade increased.

The relationship between MMP-7 grade and staining morphology is detailed in Table 5.

Table 5. Association between MMP-7 grade and histomorphological staining pattern

MMP-7 Grade	Weak	Moderate	Strong	Apical	Mixed	Focal	Dot-like
Grade 2	3	–	–	–	–	–	–
Grade 2.5	–	–	–	–	1	–	–
Grade 3	1	7	–	–	–	1	1
Grade 3.5	–	–	–	1	–	–	–
Grade 4	–	5	1*	–	–	–	–
Grade 4.5	–	–	1	2	–	–	–
Grade 5	–	2*	8	1	–	–	–

*Representative entries were verified against the original slide review

Representative Histopathological Findings

Figures 1–5 provide representative photomicrographs of the semiquantitative MMP-7 staining grades and the accompanying histopathological findings.

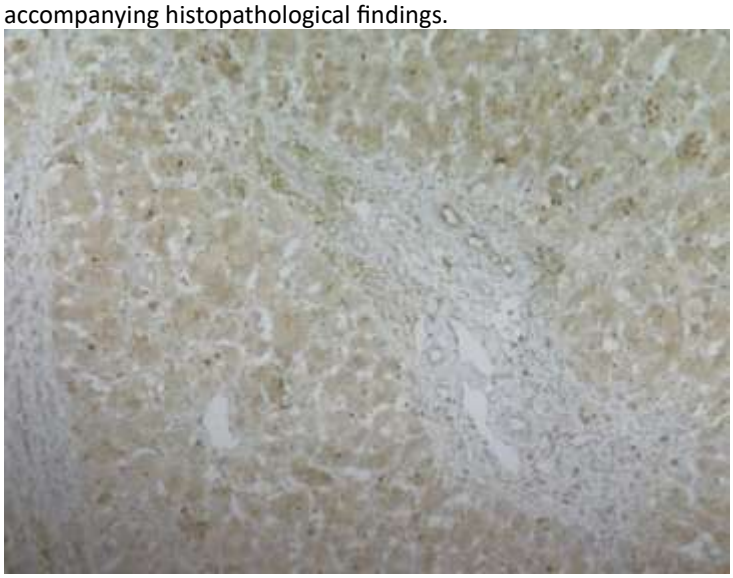

Figure 1. Representative Grade 2 MMP-7 immunohistochemical staining.

Figure 2. Representative Grade 3 MMP-7 immunohistochemical staining.

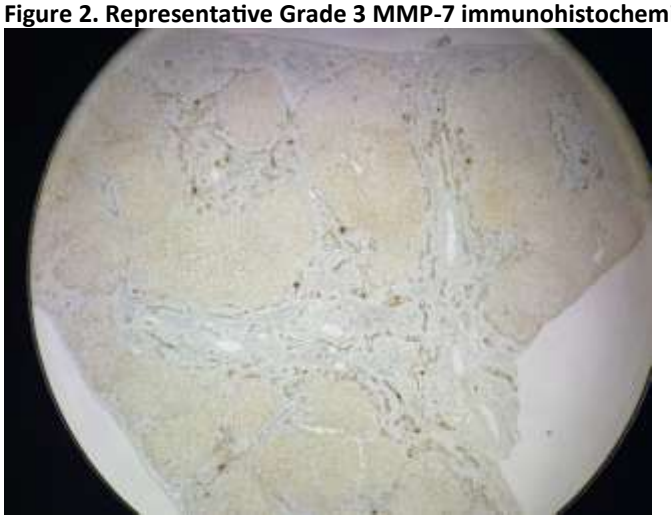

Figure 3. Representative Grade 4 MMP-7 immunohistochemical staining.

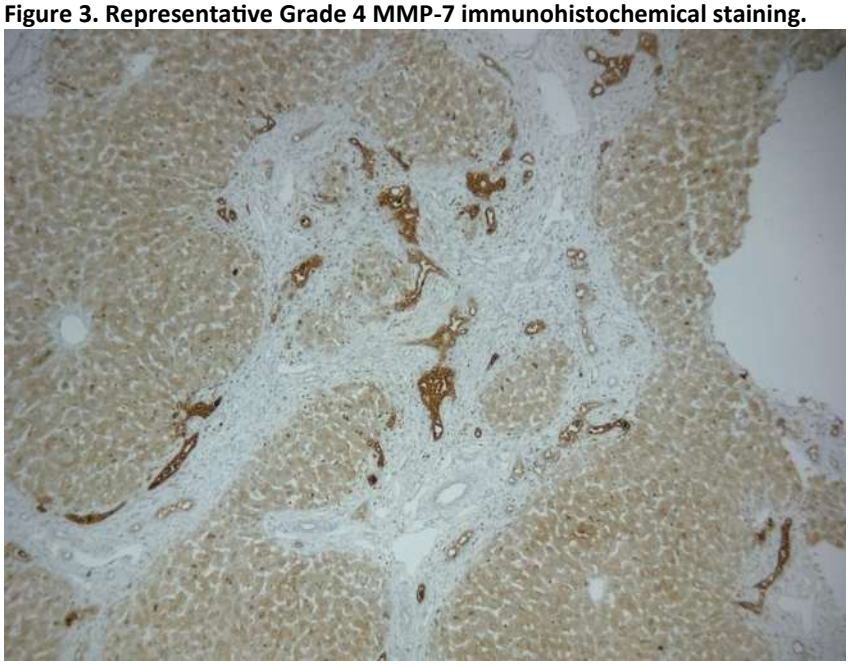

Figure 4. Representative Grade 5 MMP-7 immunohistochemical staining.

Across the illustrated grades, staining intensity increased progressively. Grade 5 sections showed diffuse, intense immunoreactivity in the bile duct epithelium.

Associated Histopathological Findings

On routine hematoxylin and eosin staining, giant cell transformation was identified in a subset of biliary atresia cases.

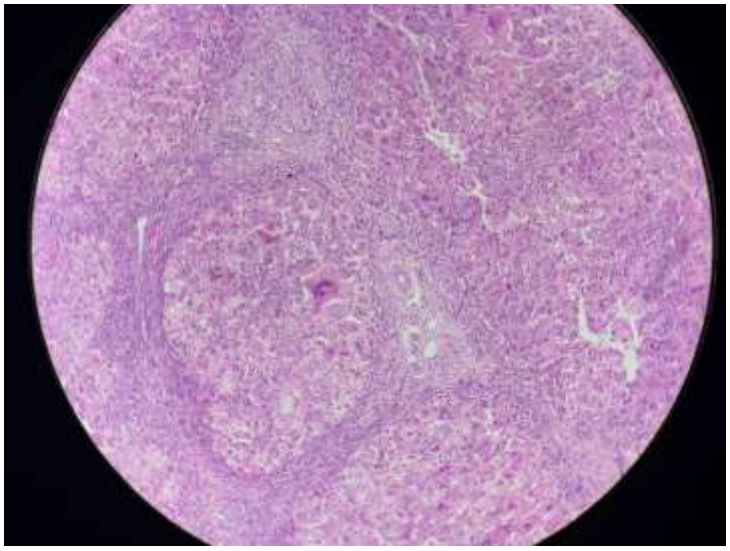

Figure 5. Representative hematoxylin and eosin-stained section showing giant cell transformation.

Giant cell transformation was recorded as an accompanying histopathological feature and did not contribute to the MMP-7 immunohistochemical grade.

Discussion

This study looked at the range of tissue MMP-7 expression and graded its presence in pediatric biliary atresia (BA). Most cases showed moderate to strong staining in the biliary epithelium, while fewer had weak or varied staining patterns such as diffuse, apical, focal, mixed, or dot-like. These results suggest that MMP-7 is regularly found in injured biliary tissue and could be a helpful marker in diagnosing BA.

Russo et al. found that bile duct proliferation, bile plugs, portal stromal edema, ductular reaction, and portal fibrosis are the main features that set BA apart from other causes of neonatal cholestasis [1]. While these features are important for diagnosis, they can overlap in early disease, making some liver biopsies less clear. In this study, tissue MMP-7 staining added value to standard assessments by showing consistent staining in most BA cases.

The importance of liver biopsy in the diagnostic work-up of neonatal cholestasis has been emphasized by several investigators. Rastogi et al. reported that preoperative liver biopsy has high diagnostic accuracy and significantly influences surgical decision-making before exploratory laparotomy [2]. Likewise, van Driel et al. confirmed that liver biopsy continues to provide valuable diagnostic information when interpreted alongside clinical and radiological findings [9]. Although Wildhaber reaffirmed that intraoperative cholangiography remains the definitive diagnostic standard for BA, its invasive nature highlights the continuing need for reliable tissue biomarkers that can improve preoperative diagnostic accuracy [10].

The biological basis for MMP-7 overexpression in BA has become increasingly clear over the past decade. Using proteomic analysis, Lertudomphonwanit et al. identified MMP-7 as one of the most significantly upregulated proteins in infants with BA, establishing it as a promising biomarker of biliary epithelial injury [11]. Subsequently, Chen et al. demonstrated increased hepatic MMP-7 expression localized predominantly to cholangiocytes, supporting the hypothesis that injured biliary epithelial cells represent the principal source of MMP-7 within the diseased liver [12]. The predominantly moderate and strong biliary epithelial staining observed in our study is consistent with these observations and further supports the role of MMP-7 in the pathogenesis of BA.

The present study demonstrated that Grade 4 and Grade 5 immunostaining constituted the predominant staining categories, indicating widespread moderate-to-strong MMP-7 expression in the biliary epithelium. In contrast, weak staining was observed in relatively few cases. These findings suggest that MMP-7 expression increases with ongoing biliary epithelial injury and ductular remodeling rather than representing a simple binary positive-or-negative immunohistochemical marker. The observed diversity of staining patterns—including diffuse, apical,

focal, mixed, and dot-like immunoreactivity—also reflects the heterogeneity of epithelial injury within different portal tracts.

To date, relatively few studies have investigated tissue MMP-7 immunohistochemistry in BA. Biswal et al. evaluated tissue MMP-7 expression in BA and other causes of neonatal cholestasis and demonstrated significantly stronger biliary epithelial staining in BA, suggesting that tissue immunohistochemistry may serve as a valuable adjunct to routine histopathological examination [27]. Our findings closely parallel those observations by confirming predominant biliary epithelial expression in BA. However, unlike the study by Biswal et al., the present study systematically categorized tissue expression using a semiquantitative grading system and documented a wider spectrum of histomorphological staining patterns. This grading approach may improve reproducibility and facilitate standardized reporting in routine surgical pathology practice.

Although tissue studies remain limited, extensive evidence supporting the diagnostic significance of MMP-7 has been generated from serum-based investigations. Dong et al. demonstrated markedly elevated serum MMP-7 concentrations in infants with BA compared with other causes of neonatal cholestasis, highlighting its potential as a non-invasive diagnostic biomarker [13]. Similar findings were reported by Yang et al., who demonstrated excellent diagnostic accuracy, with high sensitivity and specificity, for distinguishing BA from non-BA cholestatic disorders [14]. Shen et al. independently confirmed these findings in another patient cohort, reinforcing the diagnostic value of serum MMP-7 [15].

Systematic reviews and meta-analyses have made these findings even stronger. Duan et al. found that serum MMP-7 has high sensitivity and specificity for diagnosing BA, making it one of the best current biomarkers [16]. Wang et al. later confirmed these results with a larger meta-analysis, though they noted differences between study groups and lab methods [18]. On the other hand, Karbasian et al. pointed out that differences in testing methods, age-based reference values, and diagnostic cutoffs are still challenges that need to be solved before MMP-7 can be widely used [19].

The biological role of MMP-7 provides a plausible explanation for the characteristic immunohistochemical findings observed in our study. Ke et al. described MMP-7 as an important regulator of extracellular matrix remodeling, epithelial regeneration, inflammatory signaling, and biliary remodeling through multiple molecular pathways [20]. Persistent cholangiocyte injury in BA is therefore expected to stimulate increased MMP-7 production, resulting in the predominantly moderate-to-strong epithelial staining observed in our series. The localization of staining largely within bile duct epithelium also supports the concept that MMP-7 reflects active cholangiocyte injury rather than generalized hepatic inflammation.

In practice, tissue MMP-7 staining should be used alongside, not instead of, standard pathology tests. Diagnosing BA still relies on looking at known tissue features and combining them with clinical, lab, and imaging results. However, when liver biopsies are difficult to interpret because classic features are unclear, MMP-7 staining can give extra support for a BA diagnosis. The grading system used in this study also provides a useful way to improve reporting consistency and to compare results in future research.

Strengths and Limitations

This study's strengths include its systematic evaluation of tissue MMP-7 using a standard grading system and its detailed examination of staining patterns in pediatric BA. Including example images for each staining grade also makes the grading system more useful for everyday pathology work.

There are some limitations to this study. It was done at a single centre and included a modest number of patients. We did not have data on serum MMP-7 levels, liver fibrosis stage, postoperative outcomes, or long-term liver survival. Also, the grading system has not yet been tested for consistency between different observers. Larger, multicenter studies with more patients and standardized methods are needed to confirm the diagnostic and possible prognostic value of tissue MMP-7 staining.

In summary, this study shows that tissue MMP-7 staining is consistently found in the biliary epithelium of children with BA, with most cases showing moderate to strong staining and a wide range of patterns. These results support using tissue MMP-7 as an extra marker to help diagnose BA when combined with standard features. More studies at multiple centers are needed before this test can be used routinely in diagnosis.

Conclusion

The present study demonstrated consistent tissue MMP-7 immunohistochemical expression in the biliary epithelium of pediatric biliary atresia, with most cases exhibiting moderate-to-strong staining intensity. Semiquantitative grading revealed a distinct histomorphological spectrum of expression, highlighting the heterogeneity of biliary epithelial injury. These findings suggest that tissue MMP-7 immunohistochemistry may

serve as a useful adjunct to conventional histopathological evaluation and improve diagnostic confidence in challenging cases of biliary atresia.

Recommendations

Further multicenter studies with larger sample sizes are required to validate the reproducibility and diagnostic utility of the proposed semiquantitative MMP-7 grading system. Correlation of tissue MMP-7 expression with clinical outcomes, serum MMP-7 levels, and long-term prognosis may further establish its role in the pathological evaluation of pediatric biliary atresia.

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Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

Hina Aslam: Conceptualization, study design, data collection, histopathological evaluation, immunohistochemical assessment, statistical analysis, manuscript preparation.

Preethi M: Study supervision, histopathological review, interpretation of results, critical revision of the manuscript.

Mary Lilly: Histopathological review, scientific guidance, manuscript editing, and final approval.

All authors read and approved the final manuscript.

Data Availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval and Declaration

This retrospective study was approved by the Institutional Human Ethics Committee, Sree Balaji Medical College and Hospital, BIHER, Chennai (Approval No. 002/SBMC/IHEC/2025/244). The requirement for informed consent was waived due to the use of archived anonymized tissue specimens and clinical data. Generative artificial intelligence (AI) was used solely to improve the language and presentation of the manuscript. The authors reviewed, verified, and take full responsibility for all scientific content, interpretations, and conclusions.

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