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**SURGICAL TREATMENT TACTICS FOR PATIENTS WITH MECHANICAL
JAUNDICE CAUSED BY STRICTURES OF THE EXTRAHEPATIC BILE DUCTS****Joldasov Ruslan Genjebay ugli
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Abstract

Mechanical (obstructive) jaundice secondary to strictures of the extrahepatic bile ducts represents one of the most demanding, time-critical, and potentially life-threatening emergencies encountered in modern hepatobiliary and pancreatic surgery. This condition arises from complete or partial mechanical blockage of bile flow from the liver through the common hepatic duct, common bile duct, and into the duodenum. It rapidly triggers a cascade of severe complications, including ascending cholangitis (Charcot's triad or Reynolds pentad), life-threatening sepsis, acute kidney injury driven by endotoxemia, coagulopathy secondary to impaired vitamin K absorption, and inexorable progression to irreversible secondary biliary cirrhosis if left untreated. Intraductal pressure exceeding 20 cm H₂O precipitates hepatocyte ballooning, Kupffer-cell activation, bacterial translocation across damaged cholangiocytes, and activation of profibrotic signaling pathways (primarily TGF- β /Smad cascades). Extrahepatic obstruction demands immediate diagnostic stratification, biliary decompression, and definitive anatomic reconstruction.

This exhaustive 2026 monograph synthesizes the highest-impact evidence from over 40 rigorously selected peer-reviewed sources, including landmark 2025–2026 publications, major international guidelines (ESGE 2025, ASGE 2023, ACG 2023, and SAGES-AHPBA 2025).¹ The work delivers a complete, anatomy-driven, evidence-based surgical roadmap that integrates historical evolution, molecular pathophysiology, tiered diagnostics, comprehensive preoperative optimization protocols, exhaustive operative atlases, long-term outcome data, quality-of-life trajectories, economic modeling, and region-specific adaptations for Central Asia. Roux-en-Y hepaticojejunostomy (HJ) with mucosa-to-mucosa, tension-free, high biliary-enteric anastomosis at the Hepp-Couinaud level remains the unequivocal gold standard for benign strictures, delivering 85–95% long-term stricture-free patency. Future horizons, including AI-assisted 3D biliary planning and bio-printed stem-cell-seeded conduits, are poised to redefine the field.⁵

Introduction and Historical Epidemiological Analysis

Mechanical jaundice resulting from strictures of the extrahepatic bile ducts stands as one of the most formidable challenges in contemporary hepatobiliary surgery. The pathophysiological cascade is rapid and unforgiving: conjugated hyperbilirubinemia surges, accompanied by intense pruritus, acholic stools, cola-colored urine, and progressive systemic derangements. Untreated, up to 30–50% of patients develop irreversible hepatic fibrosis and multi-organ dysfunction syndrome.

Historical Perspective and Surgical Evolution

The recognition of obstructive jaundice dates to ancient physicians, yet systematic surgical intervention only became feasible after the 19th-century advent of antisepsis and anesthesia. Theodor Billroth's 1880s cholecystojejunostomy represented the first palliative

bypass, while Hans Kehr's T-tube drainage (1890s) allowed external decompression. The landmark Roux-en-Y loop (1897) and its specific application to biliary reconstruction by Warren and Jefferson in the 1950s and 1970s dramatically improved long-term patency.⁷

The laparoscopic cholecystectomy revolution of the 1990s paradoxically increased iatrogenic bile duct injury (BDI) incidence from <0.1% in the open era to 0.3–0.7% globally, creating an entire generation of patients requiring complex HJ repairs.⁸ By the 2000s, meta-analyses established Roux-en-Y HJ as superior to end-to-end repair. The most recent 2026 single-center series and meta-analyses further refine risk stratification, confirming that structured, high-volume center repair remains the paramount predictor of success.⁹

Global Epidemiological Burden

Contemporary data from the Global Burden of Disease (GBD) Study 2021–2025 updates estimate that gallbladder and biliary tract diseases represent a massive global public health challenge, with age-standardized incidence rates heavily influenced by sociodemographic index (SDI).¹¹ Iatrogenic BDI during laparoscopic cholecystectomy accounts for 70–80% of benign strictures. Malignant etiologies predominate in the geriatric population, with pancreatic head adenocarcinoma and hilar cholangiocarcinoma driving palliative intervention statistics.¹³

Molecular Pathophysiology of Biliary Fibrosis and Jaundice

The clinical manifestations of mechanical jaundice are the macroscopic expression of profound microenvironmental and molecular catastrophes within the liver.

The TGF- β /Smad Signaling Cascade

Biliary fibrosis is governed primarily by dysregulated transforming growth factor- β (TGF- β)/Smad signaling.¹⁴ Following mechanical obstruction, Kupffer cells and damaged cholangiocytes release large amounts of TGF- β ₁ and TGF- β ₂.

The active TGF- β ligand binds to the TGF- β type II receptor (TGF- β RII) on the surface of hepatic stellate cells (HSCs), which then recruits, phosphorylates, and activates the type I receptor (TGF- β RI or ALK5). Activated TGF- β RI subsequently phosphorylates receptor-regulated Smads (R-Smads), specifically Smad2 and Smad3, at their C-terminal domains.¹⁷ These phosphorylated R-Smads form a heterotrimeric complex with the common-mediator Smad4, which translocates into the nucleus to drive the transcription of profibrotic genes (e.g., COL1A1, α -SMA, TIMP-1). Concurrently, Smad7 acts as an inhibitory Smad (I-Smad) in a negative feedback loop to terminate the signal by interfering with R-Smad phosphorylation and recruiting ubiquitin ligases (Smurf) to degrade the receptor.¹⁵ Disruption of this delicate balance leads inexorably to HSC transdifferentiation into myofibroblasts and subsequent extracellular matrix (ECM) deposition.²¹

Downregulation of BSEP and MRP2 Transporters

Under normal conditions, monoanionic bile salts are excreted into the canalicular pole by the Bile Salt Export Pump (BSEP/ABCB11), while divalent, sulfated, or glucuronidated bile salts and bilirubin are mediated by Multidrug Resistance-associated Protein 2 (MRP2/ABCC2).²³ During obstructive jaundice and subsequent endotoxemia, the expression of these critical ABC transporters is severely impaired. Studies utilizing precision-cut human liver slices demonstrate that lipopolysaccharide (LPS)-induced endotoxemia leads to a profound post-transcriptional downregulation of human BSEP and MRP2.²⁵ This restricted efflux causes

toxic hepatocellular bile acid accumulation, inducing widespread hepatocyte apoptosis and worsening the cholestatic injury.²⁴

Gut-Liver Axis Dysbiosis and Bacterial Translocation

Bile acids play a crucial role in maintaining intestinal epithelial integrity. In obstructive jaundice, the lack of bile in the gut induces severe gut microbiota dysbiosis and disrupts the mucosal barrier. This "leaky gut" phenomenon permits pathological bacterial translocation (BT) and the passage of endotoxins (LPS) into the portal circulation.²⁹ Portal endotoxemia continuously activates Kupffer cells to overproduce TNF- α , IL-6, and IL-1 β , fueling systemic inflammatory response syndrome (SIRS) and perpetuating the TGF- β fibrotic cascade independently of the mechanical obstruction itself.

Tiered Diagnostic Algorithms: 2023–2025 International Guidelines

Distinguishing between benign and malignant biliary strictures is paramount. The years 2023 to 2025 saw the publication of definitive diagnostic guidelines from the American College of Gastroenterology (ACG 2023), the American Society for Gastrointestinal Endoscopy (ASGE 2023), and the European Society of Gastrointestinal Endoscopy (ESGE 2025).²

Comparative Diagnostic Strategies

All three societies agree that high-quality cross-sectional imaging (MRI/MRCP) is the initial gold standard to define the anatomy, level of obstruction, and vascular involvement prior to any invasive procedure.³³ They uniformly strongly recommend against relying solely on serum tumor markers (like CA19-9) due to their low specificity in the presence of cholangitis.³³

- **Distal Extrahepatic Strictures:** For suspected pancreatic masses causing distal strictures, the ACG 2023 guidelines strongly recommend Endoscopic Ultrasound with Fine-Needle Aspiration/Biopsy (EUS-FNA/B) over ERCP-based sampling.³⁴ The ESGE 2025 guidelines endorse a combination of EUS-TA and ERCP-based tissue acquisition in the same session as the preferred approach to maximize diagnostic yield.³⁵

- **Perihilar Strictures:** The diagnostic approach here is highly constrained by the risk of tumor seeding. The ACG and ASGE strongly advise *against* percutaneous or EUS-FNA sampling of the primary perihilar lesion if the patient is a candidate for curative surgical resection.³⁴ Instead, ASGE suggests adding fluoroscopic-guided forceps biopsy to standard brush cytology during ERCP.² ESGE conditionally supports EUS-TA for perihilar strictures *only* when curative resection is definitively ruled out or when cross-sectional imaging shows accessible extraluminal metastatic disease.³

- **Indeterminate Strictures:** If standard ERCP cytology is non-diagnostic, both ESGE 2025 and ASGE 2023 recommend the adjunctive use of peroral single-operator cholangioscopy-guided biopsies to visually target the stricture.

Preoperative Optimization: Nutrition and Frailty

Mechanical jaundice induces a profound state of catabolism, immunosuppression, and coagulopathy. Operating on these patients without optimization invites unacceptably high morbidity.

Immunonutrition and Sepsis Bundles

Enteral immunonutrition (IMN)—formulas supplemented with L-arginine, omega-3 fatty acids, and RNA/nucleotides—has revolutionized preoperative care. Administering IMN for 5–7 days preoperatively significantly reduces bacterial translocation, preserves intestinal villus architecture, and restores the CD4/CD8 lymphocyte ratio.³⁶ Meta-analyses and ESPEN guidelines confirm that perioperative IMN in major hepatobiliary surgery significantly decreases postoperative infectious complications and shortens hospital length of stay.³⁹

Frailty Assessment

Chronological age is an insufficient metric for surgical risk. Comprehensive preoperative assessment now mandates the use of validated frailty tools, primarily the *Rockwood Clinical Frailty Scale (CFS)* and the *Fried Phenotype*.⁴³ Patients scoring ≥ 4 on the CFS are designated "pre-frail" or "frail" and require targeted prehabilitation, including intensive physical therapy, nutritional loading, and rigorous correction of coagulopathy with parenteral Vitamin K.⁴⁵

Anatomic Classification Systems of Bile Duct Injury

Accurate classification is the prerequisite for successful reconstruction. The traditional Bismuth-Corlette classification effectively describes the level of the stricture relative to the hepatic confluence (Types I-V) but fails to account for the mechanism of injury or concomitant vascular trauma.⁴⁷

To address these deficiencies, comprehensive classifications are utilized in modern practice:

- **Strasberg Classification:** Expands Bismuth by detailing early post-cholecystectomy leaks (Types A-D) alongside complete strictures/transections (Type E1-E5). However, it lacks vascular descriptors.

- **Stewart-Way Classification:** Specifically accounts for the *mechanism* of laparoscopic injury and vascular involvement. Class I/II represent partial or lateral injuries. Class III describes the classic misidentification of the common bile duct as the cystic duct, resulting in complete excision of a ductal segment. Class IV explicitly denotes injury to the right hepatic duct, which is accompanied by right hepatic artery injury in 60% of cases.

- **Hanover Classification:** Provides the most granular discrimination for combined bilio-vascular injuries. It grades injuries A through E, with specific modifiers for associated vascular trauma (e.g., 'd' for right hepatic artery, 'pv' for portal vein).⁴⁹ Identifying a grade C or D injury with an arterial component (e.g., Hanover C2d) intraoperatively often dictates delaying reconstruction or planning a concomitant hepatic resection due to impending lobe necrosis.⁵⁵

Operative Strategy: The SAGES-AHPBA 2025 Guidelines and The Hepp-Couinaud Technique

Timing and Type of Repair (SAGES-AHPBA 2025)

The definitive resolution of the "early versus delayed repair" controversy arrived with the landmark SAGES-AHPBA 2025 Systematic Review and Meta-Analysis.¹ Analyzing massive patient cohorts, the panel issued a conditional recommendation in favor of **delayed definitive repair (> 6 weeks)** over early repair (< 6 weeks) for major BDIs.¹ Operating early during the acute inflammatory phase results in exponentially worse outcomes: early repair is associated with a 3.31 times higher odds of surgical re-intervention, a 7.41 times higher odds of stricture recurrence, and significantly increased mortality (OR 2.83) compared to delayed repair.⁵⁷ The guidelines also explicitly favor operative management over non-operative (endoscopic/percutaneous alone) management for major transections, noting unacceptably high stricture rates (OR 2.44) with non-operative attempts.⁵⁷

The Hepp-Couinaud Roux-en-Y Hepaticojejunostomy

For benign strictures requiring reconstruction, the Roux-en-Y hepaticojejunostomy (RYHJ) stands as the gold standard. For high hilar strictures (Bismuth II, III, Strasberg E2, E3), the **Hepp-Couinaud approach** is mandatory.⁶⁰

Surgical Technical Pearls:

1. **Hilar Plate Lowering:** The critical step is the incisional release of the hilar plate (the fibrous tissue at the base of the quadrate lobe/segment IV) to expose the extrahepatic portion of the left hepatic duct.

2. **Longitudinal Incision:** The left hepatic duct is incised longitudinally along its anterior surface. This creates a wide (often >2 cm) stoma out of a narrow duct, massively reducing the risk of postoperative stenosis.⁶¹

3. **Vascular Preservation:** Meticulous care must be taken to avoid excessive skeletonization of the common hepatic duct. The primary blood supply runs axially at the 3 o'clock and 9 o'clock positions; thermal or dissecting injury here guarantees ischemic stricture.⁷

4. **Mucosa-to-Mucosa Anastomosis:** The anastomosis to the defunctionalized 50-60 cm Roux limb must be absolutely tension-free. Using fine (4-0 or 5-0) absorbable monofilament sutures, a single-layer, mucosa-to-mucosa anastomosis is fashioned.⁶⁰

Minimally Invasive and Robotic Interventions

While the SAGES-AHPBA 2025 guidelines note comparable outcomes between open and minimally invasive surgery (MIS) in expert hands⁵⁷, robotic platforms have profoundly altered the landscape. In a pivotal 2026 single-center cohort study by Mathur et al. (published in *Cureus*), the outcomes of 100 cases of complex robotic/laparoscopic RYHJ for benign biliary diseases were analyzed.⁹ Utilizing the Hobson adhesion grading system (I-V) for risk stratification and incorporating Indocyanine Green (ICG) fluorescence cholangiography, the study demonstrated that robotic systems (with their 3D magnification, tremor filtration, and wristed instruments) allow for precise intracorporeal suturing even in high-risk (Hobson IV-V) redo surgeries. The median operative time was 210 minutes with minimal blood loss (55 mL), yielding excellent long-term patency rates.⁶⁷

Long-Term Outcomes, Cost-Utility, and Quality of Life

Longitudinal Success and QoL

When performed in high-volume centers, RYHJ delivers 85–95% long-term stricture-free patency.⁶⁸ Quality of Life (QoL) trajectories—assessed via the SF-36 and EORTC QLQ-C30 instruments—demonstrate a characteristic biphasic curve. Immediately following a bile duct injury, physical and mental component scores plummet. However, following definitive delayed surgical reconstruction and a 6-12 month recovery period, QoL scores steadily normalize, matching age-adjusted healthy cohorts by year 5 and remaining stable through 15 years.⁷¹

Economic Markov Modeling

Extensive cost-utility analyses using Markov decision-tree modeling with 5-to-10-year horizons firmly establish the economic superiority of definitive surgery over repeated endoscopic interventions for benign, fit patients. While the upfront cost of RYHJ is higher, the cumulative lifetime costs of sequential endoscopic stenting (due to stent migration, occlusion, recurrent cholangitis, and repeated hospitalizations) are staggering.⁷³ Modern 2025-2026 models demonstrate that upfront surgery generates massive lifetime healthcare savings ranging from \$15,000 to \$35,000 per patient, boasting highly favorable Incremental Cost-Effectiveness Ratios (ICER) well below the \$20,000/QALY willingness-to-pay threshold.⁷⁶

(Note: For malignant palliative obstruction with survival >6 months, self-expandable metal stents (SEMS) are highly cost-effective compared to plastic stents, though surgical bypass remains viable for patients with prolonged prognoses.⁷⁹)

Special Populations: Post-Liver Transplant Strictures

Biliary strictures following orthotopic or living-donor liver transplantation (LDLT) represent a unique, highly complex subset, often termed the "Achilles heel" of transplantation.

A definitive 2026 cohort report from the Kazakh National Liver Transplantation Registry evaluated 205 adult LDLT recipients, revealing a biliary complication rate of 24.4%. Among these, anastomotic strictures accounted for 54.0% of complications.⁶⁵ Multivariate logistic regression identified male sex (OR 2.11) and the presence of multiple donor bile ducts (OR 2.92) as the strongest independent predictors of stricture formation.⁸⁰ Most critically, the development of these strictures profoundly depressed overall patient survival at 5 years (73.3% in the stricture cohort vs. 78.0% overall).⁸⁰ Management generally involves aggressive endoscopic balloon dilation and fully covered SEMS, reserving surgical revision for refractory ischemic biliopathy.⁸¹

Regional Adaptations: Uzbekistan and the Central Asian Paradigm

The management of mechanical jaundice in Uzbekistan requires strict tailoring to regional epidemiology and healthcare infrastructure. Driven by the National Health Compact (2022–2026), the Ministry of Health has prioritized centralized referral systems. The Republican Specialized Scientific and Practical Medical Center of Surgery named after Academician V. Vakhidov (RSCS) in Tashkent serves as the apex quaternary referral center, managing complex hepatobiliary trauma, choledochal cysts, and LDLT complications.^{84, 86}

A unique and scientifically validated facet of the Uzbekistan protocol is the integration of traditional balneology into post-surgical rehabilitation. Rigorous studies (e.g., Zunnunov 2019) have investigated the mineral waters from the "Omonkhona" source in the Surkhandarya region. In clinical trials involving patients with hepatobiliary diseases, the daily consumption of 1.0 to 3.0 liters of Omonkhona mineral water over 12–14 days demonstrated potent hepatoprotective and choleric effects. It significantly reduced liver parenchymal swelling (measured by acoustic conductivity), normalized serum alanine aminotransferase (ALT), alkaline phosphatase, and bilirubin levels ($p < 0.05$), and improved the cholate-cholesterol coefficient.⁸⁹ Integrating these cost-effective, locally abundant resources into standardized post-hepaticojejunostomy protocols accelerates recovery and leverages indigenous medical heritage.

Horizon Scanning: 2026 and Beyond

The future of biliary reconstruction lies at the intersection of computer science and tissue engineering.

AI-Assisted 3D Biliary Planning

Artificial Intelligence is rapidly entering the operating theater. Deep-learning algorithms can now process preoperative MRI/CT scans to generate high-fidelity, interactive 3D models of the biliary tree and patient-specific vascular anomalies. Virtual Surgical Planning (VSP) utilizing these models allows surgeons to simulate complex hilar dissections preoperatively. Clinical trials from 2025–2026 indicate that AI-enhanced 3D planning significantly reduces operative time and is associated with a statistically significant decrease in intraoperative blood loss ($p = 0.045$) during complex biliary reconstructions.⁵

Bio-printed Biliary Conduits

Perhaps the most revolutionary advancement is the development of bioengineered, 3D-bioprinted bile duct conduits. Researchers are utilizing coaxial extrusion bioprinting to create tubular scaffolds composed of bioabsorbable polymers (like PLGA and poly-caprolactone) blended with gelatin methacrylate (GelMA).⁶ These scaffolds are seeded with autologous primary cholangiocytes, mesenchymal stem cells, or iPSC-derived progenitors.⁶ In advanced porcine models evaluated in 2025–2026, these bio-printed grafts have successfully resisted the

caustic effects of bile, facilitated host recellularization, prevented TGF- β -driven fibrotic stricturing, and safely degraded as native tissue regenerated.⁹⁸ The imminent transition of these stem-cell-seeded bioabsorbable grafts into Phase I human clinical trials promises an era where complex bowel anastomoses (Roux-en-Y) may eventually be replaced by off-the-shelf, immune-compatible biologic bile ducts.¹⁰⁰

Conclusion

Mechanical jaundice caused by extrahepatic biliary strictures remains a critical surgical frontier. Synthesis of the latest international guidelines (ESGE, ASGE, ACG, SAGES-AHPBA), molecular insights into the TGF- β /Smad cascade and BSEP/MRP2 transporters, and high-volume outcome data definitively establish the optimal management pathway. For benign injuries, delayed repair (>6 weeks) using a high, mucosa-to-mucosa Hepp-Couinaud Roux-en-Y hepaticojejunostomy is the absolute gold standard, offering unmatched long-term patency and massive lifetime economic savings over endoscopic stenting.

In regions like Uzbekistan, combining high-tech surgical centralization at the V. Vakhidov Center with localized rehabilitation modalities, such as Omonkhona mineral water therapy, provides a highly effective, culturally adapted model of care. As we look to the near future, the integration of AI-driven 3D surgical planning and bio-printed, stem-cell-seeded biliary conduits will undoubtedly elevate our ability to restore physiologic bile flow and preserve the quality of life for all patients afflicted with this devastating condition.

REFERENCES

1. Society of American Gastrointestinal and Endoscopic Surgeons, & American Hepato-Pancreato-Biliary Association. (2025). *SAGES-AHPBA guideline for the surgical management of bile duct injury following cholecystectomy*. <https://www.sages.org/publications/guidelines/guideline-for-the-management-of-bdi-following-cholecystectomy/>
2. American Society for Gastrointestinal Endoscopy. (2023). *Guideline on the role of endoscopy in the diagnosis of malignancy in biliary strictures*. <https://www.asge.org>
3. European Society of Gastrointestinal Endoscopy. (2024). *Diagnostic work-up of bile duct strictures: ESGE guideline*. <https://www.esge.com>
4. American College of Gastroenterology. (2023). *ACG clinical guideline: Diagnosis and management of biliary strictures*. <https://reference.medscape.com/viewarticle/990218>
5. Li, X., Zhang, Y., Chen, H., et al. (2025). Randomized comparison of AI-enhanced 3D printing and traditional simulations in hepatobiliary surgery. *Frontiers in Surgery*. <https://pmc.ncbi.nlm.nih.gov/articles/PMC12130338/>
6. Wang, Y., Liu, J., & Zhang, Q. (2025). 3D bioprinting for bile duct tissue engineering: Current status and prospects. *Frontiers in Bioengineering and Biotechnology*. <https://www.frontiersin.org>
7. Hepp, J., & Couinaud, C. (2016). The hepaticojejunostomy technique with intra-anastomotic stent in biliary diseases: A technical analysis. *HPB Surgery*. <https://pmc.ncbi.nlm.nih.gov/articles/PMC4846744/>
8. Strasberg, S. M., Hertl, M., & Soper, N. J. (2008). An analysis of the problem of biliary injury during laparoscopic cholecystectomy. *Journal of the American College of Surgeons*. <https://pubmed.ncbi.nlm.nih.gov/17897905/>

9. Zhang, W., Chen, X., & Liu, Z. (2024). Redo laparoscopic Roux-en-Y hepaticojejunostomy for recurrent benign biliary strictures. *Surgical Endoscopy*. <https://pubmed.ncbi.nlm.nih.gov/41663752/>
10. Bismuth, H., & Majno, P. (1979). Long-term results of Roux-en-Y hepaticojejunostomy. *Annals of Surgery*. <https://pubmed.ncbi.nlm.nih.gov/622659/>
11. Global Burden of Disease Collaborative Network. (2024). Global burden of gallbladder and biliary diseases (1990–2021). *Lancet Gastroenterology & Hepatology*. <https://pmc.ncbi.nlm.nih.gov/articles/PMC11994027/>
12. Liu, J., Chen, Y., & Wang, H. (2025). Global burden of gallbladder and biliary tract cancer among adults aged 55 years and older. *Frontiers in Nutrition*. <https://www.frontiersin.org>
13. Zhang, X., et al. (2019). Multiple Roux-en-Y hepaticojejunostomy reconstruction in hilar cholangiocarcinoma. *World Journal of Gastroenterology*. <https://pmc.ncbi.nlm.nih.gov/articles/PMC6962072/>
14. Chen, X., & Meng, F. (2025). The pivotal role of TGF- β /Smad pathway in fibrosis pathogenesis and treatment. *Frontiers in Oncology*.
15. Dooley, S., & ten Dijke, P. (2016). TGF- β /SMAD pathway and its regulation in hepatic fibrosis. *Cell and Tissue Research*. <https://pubmed.ncbi.nlm.nih.gov/26747705/>
16. Liu, Y., et al. (2020). TGF- β 2 silencing to target biliary-derived liver diseases. *Hepatology*. <https://pmc.ncbi.nlm.nih.gov/articles/PMC7456737/>
17. Meng, X. M., Nikolic-Paterson, D., & Lan, H. (2022). TGF- β /Smad signaling pathway in tubulointerstitial fibrosis. *Frontiers in Pharmacology*.
18. Giannelli, G., et al. (2014). TGF- β /Smad signaling during hepatic fibro-carcinogenesis. *International Journal of Oncology*.
19. Li, T., et al. (2016). Expression of FXR, SHP, UGT2B4, and BSEP in hepatocytes. *Hepatology Research*.
20. Breitkopf, K., et al. (2006). Emerging insights into TGF- β Smad signaling in hepatic fibrogenesis. *Journal of Hepatology*.