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Etiology and Clinical Features of Secondary Sclerosing Cholangitis: A Single-Center Retrospective Study From 2016 to 2024

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Keywords: etiology | liver transplantation | primary sclerosing cholangitis | prognosis | secondary sclerosing cholangitis

ABSTRACT

Aims: Secondary sclerosing cholangitis (SSC) is a rare progressive biliary disease. We aimed to analyze the underlying causes, treatment approaches, and prognosis of SSC in order to enhance awareness of this disease.

Methods: A retrospective analysis was conducted on patients diagnosed with SSC in a single tertiary center in China between October 2016 and March 2024, focusing on the etiology, treatment modalities, and follow-up outcomes. Clinical outcomes were compared to patients with primary sclerosing cholangitis during the same period.

Results: A total of 21 patients were included in the study, with a median age of 42 (interquartile range 34, 57). The primary causes of SSC included surgical injury (seven cases, 33.3%) and drug-induction (six cases, 28.6%). Eight patients (38.1%) underwent ERCP, six patients (28.6%) received PTCD, and two patients (9.5%) underwent choledochoscopic bile duct dilation or stone extraction.Median follow-up time was 13 (interquartile range 10, 35) months, during which five patients (23.8%) died and five patients (23.8%) underwent liver transplants.Comparison of patients who received biliary decompression interventions and patients who did not revealed no significant difference in prognosis ($p = 0.45$). The median time of transplant-free survival was 35 months in the SSC group compared with 67 months in the PSC group. A trend toward a worse prognosis was observed in SSC compared to PSC ($p = 0.13$).

Conclusions: SSC is a complex disease with varied etiologies and poor prognosis, particularly when caused by bile duct surgical trauma. Bile duct decompression like ERCP does not offer long-term survival benefits. SSC exhibited a trend towards a less favorable prognosis compared to PSC.

1 | Introduction

Secondary sclerosing cholangitis (SSC) is a rare progressive biliary disease characterized by chronic inflammation and fibrosis of the bile ducts, leading to bile stasis and ultimately liver failure. The etiology of SSC is diverse, commonly including chronic biliary obstruction, infection, drug toxicity, ischemic injury, and biliary surgical trauma [1]. SSC is often diagnosed at an advanced stage due to its nonspecific early symptoms, which limits the effectiveness of treatment. Although SSC shares similar pathological features with primary sclerosing cholangitis (PSC), its disease course is more aggressive, with poorer prognosis [2]. Many patients with SSC ultimately require liver transplantation (LT) as a definitive treatment [1]. Therefore, accurately

identifying the underlying causes of SSC is crucial for optimizing diagnostic accuracy and therapeutic strategies.

Recent studies have indicated that biliary surgical injury and bile duct stones are the major contributing factors to SSC. A study from the Mayo Clinic found that the prognosis of patients with SSC varies significantly depending on the underlying cause. Patients with SSC secondary to surgical injury typically have worse outcomes, whereas those with SSC secondary to bile duct stones tend to fare better [2]. Additionally, drug-induced SSC has gained increasing attention, particularly, in relation to immune checkpoint inhibitors (ICIs) and certain chemotherapeutic agents, which may induce SSC through mechanisms involving ischemic injury to the bile duct epithelium or immune-mediated pathways [3, 4].

In this study, we aimed to explore the clinical characteristics, treatments, and outcomes associated with different etiologies of SSC. We also compared the prognosis of SSC with PSC. Our goal was to offer guidance for the early identification and clinical management of SSC.

2 | Methods

2.1 | Study Population

We conducted a retrospective analysis of patients diagnosed with SSC at Beijing Friendship Hospital, affiliated with Capital Medical University, from October 2016 to March 2024. The diagnostic criteria for SSC included: (1) imaging findings from ERCP and/or MRCP showing multifocal biliary strictures, segmental dilation, and a beaded or "pruned tree" appearance of the biliary system; (2) elevated biochemical markers such as alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT), and/or clinical manifestations of cholestasis; (3) identification of secondary causes, including chronic biliary obstruction, infectious diseases, drug toxicity, ischemic biliary injury, or immune-mediated etiologies. Patients with IgG4-related sclerosing cholangitis, post-LT SSC, or those with a history of cholecystectomy without documented intraoperative biliary manipulation were excluded from this study. Diagnosis of PSC was made in the presence of typical findings of sclerosing cholangitis and compatible liver biopsy histology with cholestatic features, after excluding secondary causes.

2.2 | Data Collection

Clinical data were retrospectively collected, including demographic information, clinical presentations (such as symptoms, time to diagnosis), underlying etiologies, laboratory findings, imaging results, histopathological characteristics, therapeutic interventions, and outcomes. Data were extracted from electronic medical records, with a focus on analyzing the disease progression and treatment efficacy. Imaging studies, histological samples, and surgical records were reviewed to confirm diagnoses and assess related factors. Outcomes include death, LT, waiting for LT, and alive. Endpoints were time from diagnosis to either death or LT, and number of deaths or LT. Follow-up methods include outpatient medical records and telephone follow-ups.

2.3 | Statistical Analysis

All data were analyzed using SPSS version 25.0. Descriptive statistics were employed for data analysis. Continuous variables with normal distribution were expressed as mean ± standard deviation (SD), while non-normally distributed variables were expressed as median (interquartile range). Survival free of liver transplantation was estimated using the Kaplan–Meier method. Comparison of survival were performed using log-rank test between SSC and PSC, SSC treated with bile duct decompression (ERCP, PTCD, and choledochoscopic bile duct dilation) and SSC with no such intervention. A two-tailed p value < 0.05 was considered statistically significant.

3 | Results

3.1 | Demographics and Clinical Characteristics

As shown in Table 1, a total of 21 patients with SSC were included in this study, comprising 11 males (52.4%) and 10 females (47.6%). The age at diagnosis ranged from 6 to 80 years, with an average age of 42.9 years. The follow-up duration for all patients was 13 (10, 35) months. During the follow-up period, five patients died, and five patients underwent LT. No patients were lost to follow-up. The time from diagnosis to death or LT was 12.5 (9.25, 27.5) months. Among the 21 patients, 18 (85.7%) presented with

TABLE 1 | Demographics and clinical characteristics.

Characteristic	Number
Total number of cases	21
Gender(male), *n* (%)	11 (52.4%)
Age at diagnosis, mean ± SD	42.9 ± 19.7
Clinical symptoms	
Jaundice	18 (85.7%)
Abdominal discomfort	13 (61.9%)
Pruritus	9 (42.9%)
Fever	7 (33.3%)
Etiology of SSC	
Postoperative complications	7 (33.3%)
Drugs	6 (28.6%)
Infections	3 (14.3%)
Histiocytosis	3 (14.3%)
Cancer	1 (4.8%)
Portal hypertensive cholangiopathy	1 (4.8%)
Outcome	
Dead	5 (23.8%)
Liver transplantation	5 (23.8%)
Follow-up time, months	13 (10, 35)

jaundice as the primary symptom, while 3 patients (14.3%) were diagnosed due to abnormal liver function tests. Additionally, 13 patients (61.9%) reported right upper abdominal discomfort, 9 patients (42.9%) experienced pruritus, and 7 patients (33.3%) had recurrent fever.

3.2 | Auxiliary Examinations

As shown in Figure 1, at admission, the total bilirubin (TBIL) level was 128.1 ± 108.8 μmol/L, and the direct bilirubin (DBIL) level was 69.7 ± 66.5 μmol/L. Both ALP and GGT levels were elevated to varying degrees, with ALP levels at 619.6 ± 481.0 U/L and GGT levels at 591.8 ± 608.4 U/L. All patients underwent magnetic resonance imaging (MRI), with 19 patients receiving MRCP and 2 patients undergoing contrast-enhanced abdominal MRI. Additionally, eight patients underwent ERCP.

3.3 | Etiology, Treatment, and Outcomes

As shown in Table 2, all patients received ursodeoxycholic acid therapy (15 mg/kg/day) following diagnosis.

3.3.1 | Surgery-Related SSC

Seven patients (33.3%) developed SSC secondary to surgical trauma:

- Five patients underwent cholecystectomy, choledocholithotomy, and laparoscopic common bile duct exploration (LCBDE) with T-tube drainage.
- One patient underwent resection of a congenital choledochal cyst with hepaticoenterostomy.
- One patient sustained biliary tract injury during resection of a retroperitoneal neuroblastoma.

Among these seven patients, one died from decompensated cirrhosis and multiple organ failure 10 months after SSC diagnosis. Five patients underwent interventions, including ERCP, PTCD, choledochofiberscopic bile duct dilation, bile duct exploration, and stone extraction, but two of them ultimately underwent LT 13 and 54 months after diagnosis, respectively. Two patients were awaiting LT at time of last follow-up.

3.3.2 | Drug-Related SSC

Six patients (28.6%) were diagnosed with drug-induced SSC:

- Three patients had SSC related to the use of traditional Chinese medicine (specific ingredients unknown), and two were confirmed to have drug-induced liver injury through liver biopsy. One patient underwent LT, while the other two maintained long-term stability with hepatoprotective drugs and ursodeoxycholic acid.
- One patient received chemotherapy for peritoneal mesothelioma (apatinib plus etoposide, later switched to pemetrexed plus cisplatin) and underwent PTCD, but died due to multiple organ failure (liver, heart, and kidney).
- One patient with cervical cancer received ICI therapy (pembrolizumab) and was diagnosed with decompensated cirrhosis by MRCP (shown in Figure 2). This patient underwent PTCD.
- One patient developed Stevens–Johnson syndrome and liver injury with sclerosing cholangitis after levofloxacin treatment.

3.3.3 | Recurrent Cholangitis and/or Cholelithiasis-Related SSC

Three patients (14.3%) developed SSC secondary to recurrent cholangitis and/or cholelithiasis, with follow-up durations of 18, 27, and 93 months, respectively. All patients underwent multiple ERCP and/or PTCD procedures. One patient with recurrent cholangitis had bile cultured repeatedly indicating *Pseudomonas aeruginosa* and *Enterococcus faecium*, requiring long-term drainage by PTCD and intermittent antibiotic treatment. The ERCP and MRCP findings for this patient are shown in Figure 3.

3.3.4 | Other Etiologies of SSC

- Langerhans cell histiocytosis (LCH) involving the bile ducts: Two patients (9.5%) had SSC secondary to LCH. One patient developed symptoms at age 5 and was diagnosed with decompensated cirrhosis at our hospital, later died from gastrointestinal bleeding. The other patient, who developed symptoms in adolescence, underwent ERCP with biliary stent placement and eventually required LT.

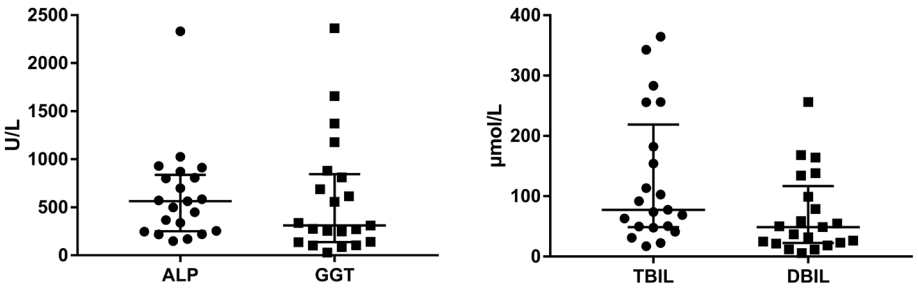

FIGURE 1 | ALP, GGT, TBIL, and DBIL of 21 cases with SSC, presented as median with interquartile range. ALP, alkaline phosphatase; DBIL, direct bilirubin; GGT, gamma-glutamyl transferase; TBIL, total bilirubin.

TABLE 2 | Etiology, intervention and outcome of 21 cases of SSC.

No	Gender	Age	Etiology of SSC	Intervention	Outcome	Follow-up time (months)[a]
1	M	43	Recurrent cholangitis	ERCP, PTCD	Alive	27
2	M	24	Drug (traditional Chinese medicine)		Alive	95
3	F	62	Drug (traditional Chinese medicine)		Alive	86
4	M	61	Pancreatic head carcinoma	ERCP	Dead (cancer)	1
5	M	39	Cholecystectomy + LCBDE	CBDD, ERCP	LT	54
6	M	35	Choledocholithiasis	ERCP	Alive	93
7	M	64	Cholecystectomy + LCBDE		Dead (decompensated cirrhosis)	10
8	F	42	Drug (pembrolizumab)	PTCD	Dead (cancer)	9
9	M	47	Drug (apatinib/etoposide)	PTCD	Dead (cancer)	2
10	F	66	Recurrent cholangitis	ERCP	Alive	18
11	F	80	Cholecystectomy + LCBDE	CBDE	Alive	53
12	F	7	Surgery (resection of retroperitoneal neuroblastoma)	ERCP	LT	13
13	F	32	Drug (traditional Chinese medicine)		LT	31
14	M	6	Histiocytosis		Dead (decompensated cirrhosis)	17
15	F	15	Surgery (resection of congenital choledochal cyst)		Waiting for LT	13
16	M	57	Histiocytosis		Alive	13
17	M	37	Portal hypertensive biliopathy	PTCD	LT	35
18	M	38	Histiocytosis	ERCP	LT	12
19	F	56	Cholecystectomy + LCBDE	ERCP, PTCD	Alive	12
20	F	34	Drug (levofloxacin)		Alive	5
21	F	56	Cholecystectomy + LCBDE	PTCD	Waiting for LT	1

Abbreviations: CBDD, choledochoscopic bile duct dilation; CBDE, common bile duct exploration; LT, liver transplantation.
[a]Follow-up time: time from diagnosis of SSC to the last follow-up or to the endpoint of the study (either death or liver transplantation).

- Non-LCH (Erdheim–Chester disease [ECD]) involving the bile ducts: One patient (4.8%) with non-LCH was treated with targeted therapy, resulting in near-normal bilirubin levels.
- Portal hypertensive biliary disease: One patient (4.8%) suffered from portal hypertensive biliopathy induced by cavernous transformation of portal vein. He underwent PTCD for recurrent cholangitis and later treated by LT.
- Pancreatic dead cancer-related SSC: One patient (4.8%) was diagnosed with pancreatic adenocarcinoma with lymph node metastasis during exploratory laparotomy. The patient developed jaundice 2 months postoperatively. ERCP at our hospital revealed a 3 cm stricture in the middle of the bile duct, and a metal-covered biliary stent was placed to relieve the obstruction. However, bilirubin levels did not decrease significantly. Follow-up ERCP showed sparse intrahepatic bile ducts with a beaded and prune-tree appearance, suggestive of SSC secondary to bile stasis due to pancreatic head cancer. The patient died after discharge.

3.3.5 | Invasive Intervention and Clinical Outcome

Over all, a total of 13 patients with SSC underwent bile duct decompression treatment, including therapeutic ERCP (ballon dilation/stent therapy/stone extraction), PTCD, or cholangioscopy-assisted biliary dilation or stone extraction. Comparison of the 13 patients who received biliary drainage interventions and the 8 patients who did not revealed no significant difference in prognosis ($p = 0.45$), shown in Figure 4A.

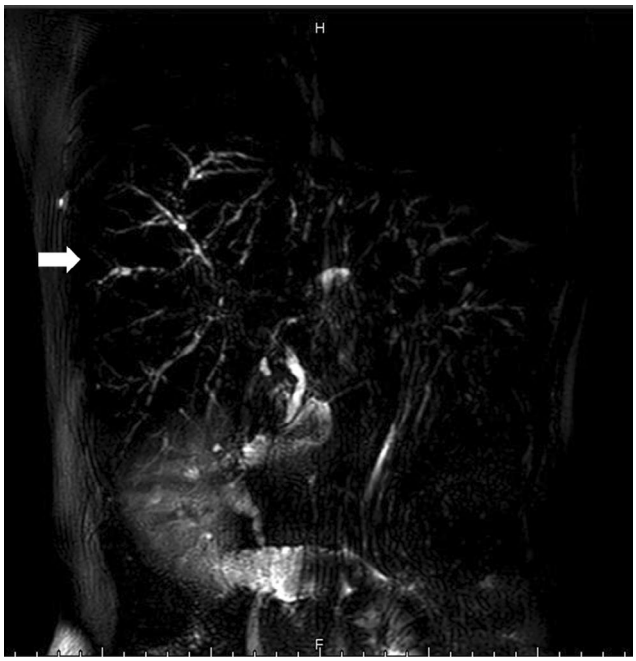

FIGURE 2 | MRCP of a 42-year-old female with pembrolizumab-induced SSC: Intrahepatic bile ducts exhibit mild dilation, displaying a beaded appearance in certain segments (arrow). Biliary tract demonstrates rigidity in its course, and there is notable stenosis of the common hepatic duct.

A total of 38 PSC patients were identified during the same period. The median time of transplant-free survival was 35 months (95% confidence interval [CI] 8.2, 61.8) in the SSC group compared with 67 months (95% CI: 50.3, 83.7) in the PSC group. Although there was no statistically significant difference between SSC and PSC, a trend towards a worse prognosis was observed in SSC compared to PSC ($p = 0.13$), especially for the first 5 years after diagnosis. K-M cumulative survival curve was demonstrated in Figure 4B. There were no cases of cholangiocarcinoma or hepatocellular carcinoma among the SSC patients during follow-up.

4 | Discussion

This study highlights the significant differences in clinical presentation, treatment, and prognosis among SSC patients with varying etiologies, providing valuable insights into this rare and challenging condition. The primary causes of SSC in this cohort were surgical bile duct injuries, which is consistent with previous studies from other medical centers [2, 5]. However, the prognosis and clinical outcomes varied based on the underlying cause, underscoring the importance of early identification and appropriate management.

Surgical interventions involving the bile ducts, such as cholecystectomy and common bile duct exploration, were identified as significant causes of SSC in this study. Among the seven patients with SSC secondary to surgical injury, the prognosis was poor. One patient died within 10 months after SSC diagnosis due to liver failure and multiple organ dysfunction, and two underwent LT within 13–54 months, with two others being referred to LT soon after diagnosis. Despite most patients underwent biliary drainage such as ERCP and PTCD, progression to end-stage liver disease was inevitable in some patients. On the other hand, seven patients had liver cirrhosis at the time of SSC diagnosis in our cohort, four of which were surgery-related. This suggests that surgical trauma-induced SSC, associated with bile duct ischemia [6], has a worse prognosis compared to other causes. Therefore, minimizing mechanical or ischemic injury to the bile ducts during surgery is critical to preventing SSC. Postoperative T-tube cholangiography and routine MRCP assessment may be necessary for early detection.

Drug-induced SSC, first reported in the 1980s [7], is another notable cause of SSC. It is thought to result from ischemic and hypoxic damage to the biliary epithelium, leading to fibrotic changes. In a study of 102 patients with drug-induced liver injury, 10 out of 25 who underwent MRCP were diagnosed with SSC, highlighting the role of drug-related biliary abnormalities in SSC pathogenesis [8]. Drugs implicated in SSC include amoxicillin-clavulanate, celecoxib, and chemotherapeutic agents [9–11], especially when delivered via hepatic artery infusion, as ischemia and toxic injury are key mechanisms [12].

With the growing use of ICIs and targeted therapies, drug-induced SSC has become more common [13]. ICIs can cause severe lymphocytic infiltration of the bile ducts, predominantly CD8+ T cells, resulting in progressive bile duct injury [14, 15]. Although immunosuppressive therapies such as corticosteroids or ERCP can be beneficial, some patients do not respond well to treatment [16, 17].

Patients with SSC secondary to recurrent biliary stones or cholangitis generally had a better prognosis, compared to surgery-related SSC. In this study, three patients were followed for 18, 27, and 93 months, respectively, without the need for LT. The chronic obstruction of the bile ducts due to stones and repeated episodes of cholangitis lead to bile stasis, which exacerbates the formation of pigment stones and inflammatory strictures [12, 18]. Multiple endoscopic or percutaneous drainage and/or stone extraction are often employed for bile stasis and intraductal stone in these cases [19]. Early intervention to relieve bile duct obstruction through may help mitigate further liver damage and prevent irreversible fibrosis.

This study also identified rare causes of SSC, such as LCH and ECD. LCH, a multisystem disorder involving the liver and bile ducts, can cause extensive bile duct destruction, leading to SSC. The prognosis for LCH with biliary involvement is generally poor, and early diagnosis with systemic treatment can help alter the disease course [20, 21]. ECD, another rare non-Langerhans histiocytosis, presents similarly but has distinct histopathological features, such as foamy macrophages infiltrating the bile ducts [22]. Recognizing these rare disease entities is essential for timely diagnosis and appropriate treatment.

Our study indicates that the prognosis of SSC patients might be worse than that of PSC patients, which makes early diagnosis more crucial. Additionally, ERCP/PTCD may not improve the long-term prognosis of patients with SSC. Therefore, close follow-up with regular imaging and liver function tests are warranted, and LT should be carried out as early as possible.

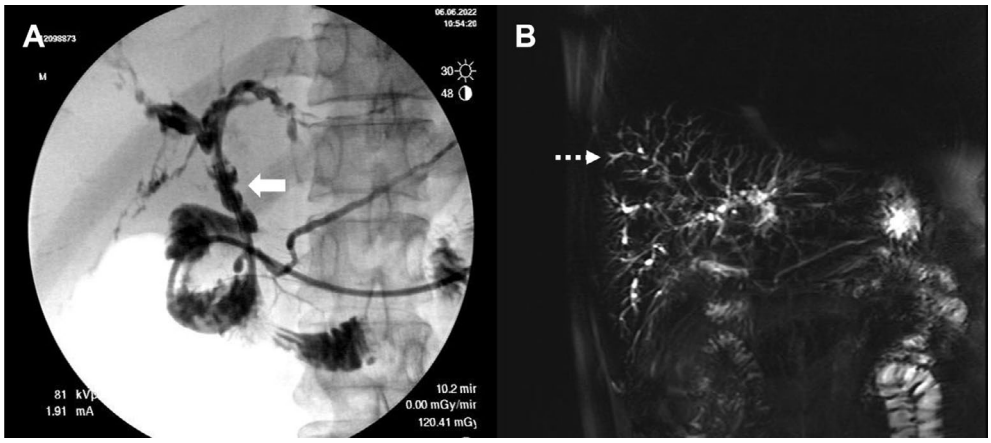

FIGURE 3 | A 43-year-old male with SSC associated with recurrent cholangitis. (A) ERCP suggests segmental dilation and focal stenosis of intrahepatic and extrahepatic bile ducts, presenting as a beaded appearance (solid arrow). (B) MRCP showed diffused thickening of bile ducts with mild dilation of the intrahepatic bile ducts, with a twig-like appearance (dashed arrow) and thickening of Glisson's sheath.

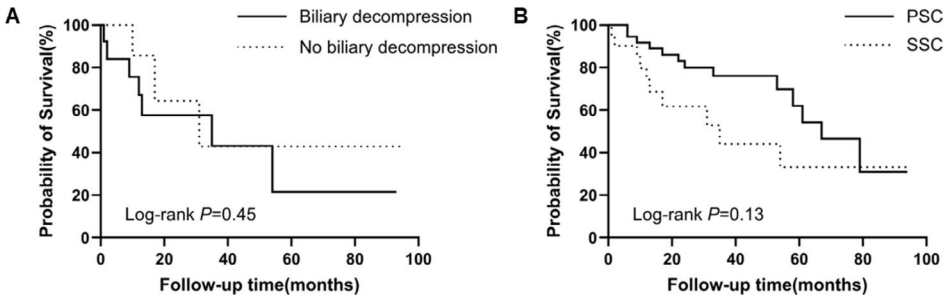

FIGURE 4 | Kaplan–Meier curve for (A) SSC patients with biliary decompression, such as ERCP, PTCD, and so forth, comparing to SSC patients without such intervention. (B) SSC compared to PSC.

This study has several limitations. First, the sample size was small, limiting the statistical power to detect significant differences between subgroups. Additionally, this was a single-center study, which may restrict the generalizability of the findings. Future research with larger, multicenter cohorts is needed to confirm these results and explore potential therapeutic interventions. Furthermore, our study did not include IgG4-related sclerosing cholangitis, which responds well to corticosteroid therapy if diagnosed early. Including this condition in future analyses could provide a more comprehensive understanding of the SSC spectrum.

5 | Conclusion

In conclusion, SSC is a rare but severe progressive disease with diverse etiologies. Surgical bile duct injuries tend to have a worse prognosis compared to SSC caused by biliary stones or cholangitis. Drug-induced SSC, particularly in the era of modern cancer therapies, is an emerging challenge, requiring heightened awareness for early diagnosis and intervention. Rare causes such as histiocytosis should also be considered in patients with unexplained cholangitis and biliary strictures. Bile duct decompression like ERCP does not offer long-term survival benefits in SSC. Comparing to PSC, SSC exhibited a trend toward a less favorable prognosis. Early recognition and treatment are essential for improving outcomes in SSC patients.

Acknowledgments

The authors have nothing to report.

Ethics Statement

The study protocol was approved by the institutional review board of the Beijing Friendship Hospital, Capital Medical University. Consents for scientific publication of images shown in this article were obtained from the patients. The study conformed to the ethical guidelines of the Helsinki Declaration.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. P. Ruemmele, F. Hofstaedter, and C. M. Gelbmann, "Secondary Sclerosing Cholangitis," *Nature Reviews. Gastroenterology & Hepatology* 6, no. 5 (2009): 287–295.

2. A. A. Gossard, P. Angulo, and K. D. Lindor, "Secondary Sclerosing Cholangitis: A Comparison to Primary Sclerosing Cholangitis," *American Journal of Gastroenterology* 100, no. 6 (2005): 1330–1333.

3. K. Ogawa, K. Kamimura, and S. Terai, "Antiprogrammed Cell Death-1 Immunotherapy-Related Secondary Sclerosing Cholangitis," *Hepatology* 69, no. 2 (2019): 914–916.

4. T. Tanaka, A. Sakai, M. Tsujimae, et al., "Delayed Immune-Related Sclerosing Cholangitis After Discontinuation of Pembrolizumab: A Case Report," *World Journal of Gastroenterology* 28, no. 28 (2022): 3732–3738.

5. C. C. Zhang, P. Sauer, and C. Rupp, "Effect of Endoscopic Treatment in Patients With Secondary Sclerosing Cholangitis," *Journal of Gastroenterology and Hepatology* 37, no. 10 (2022): 2011–2018.

6. J. Martin de Carpi, X. Tarrado, and V. Varea, "Sclerosing Cholangitis Secondary to Hepatic Artery Ligation After Abdominal Trauma," *European Journal of Gastroenterology & Hepatology* 17, no. 9 (2005): 987–990.

7. M. M. Kemeny, H. Battifora, D. W. Blayney, et al., "Sclerosing Cholangitis After Continuous Hepatic Artery Infusion of FUDR," *Annals of Surgery* 202, no. 2 (1985): 176–181.

8. H. O. Gudnason, H. K. Bjornsson, M. Gardarsdottir, et al., "Secondary Sclerosing Cholangitis in Patients With Drug-Induced Liver Injury," *Digestive and Liver Disease* 47, no. 6 (2015): 502–507.

9. Z. Zhang, L. Xu, N. Qin, et al., "Case Report: Secondary Sclerosing Cholangitis Induced by Lapatinib and Vinorelbine in a Metastasis Breast Cancer Patient," *Thorac Cancer* 12, no. 12 (2021): 1912–1916.

10. A. Kusakabe, K. Ohkawa, N. Fukutake, et al., "Chemotherapy-Induced Sclerosing Cholangitis Caused by Systemic Chemotherapy," *ACG Case Reports Journal* 6, no. 7 (2019): e00136.

11. J. Brooling and R. Leal, "Secondary Sclerosing Cholangitis: A Review of Recent Literature," *Current Gastroenterology Reports* 19, no. 9 (2017): 44.

12. D. R. Ludwig, M. A. Anderson, M. Itani, K. G. Sharbidre, N. Lalwani, and R. M. Paspulati, "Secondary Sclerosing Cholangitis: Mimics of Primary Sclerosing Cholangitis," *Abdominal Radiology* 48, no. 1 (2023): 151–165.

13. Y. Koya, M. Shibata, N. Shinohara, et al., "Secondary Sclerosing Cholangitis With Hemobilia Induced by Pembrolizumab: Case Report and Review of Published Work," *Hepatology Research* 49, no. 8 (2019): 950–956.

14. P. A. Patil and X. Zhang, "Pathologic Manifestations of Gastrointestinal and Hepatobiliary Injury in Immune Checkpoint Inhibitor Therapy," *Archives of Pathology & Laboratory Medicine* 145, no. 5 (2021): 571–582.

15. H. Kawakami, J. Tanizaki, K. Tanaka, et al., "Imaging and Clinicopathological Features of Nivolumab-Related Cholangitis in Patients With Non-small Cell Lung Cancer," *Investigational New Drugs* 35, no. 4 (2017): 529–536.

16. T. Yamamoto, K. Mizuno, T. Ito, et al., "Abdominal Pain Accompanied by Elevated Serum Inflammatory Markers and Biliary Enzymes for Diagnosing Immune Checkpoint Inhibitor-Induced Sclerosing Cholangitis," *Investigational New Drugs* 41, no. 3 (2023): 512–521.

17. Y. Hirasawa, K. Yoshimura, H. Matsui, et al., "A Case Report on Severe Nivolumab-Induced Adverse Events Similar to Primary Sclerosing Cholangitis Refractory to Immunosuppressive Therapy," *Medicine (Baltimore)* 100, no. 23 (2021): e25774.

18. R. Abdalian and E. J. Heathcote, "Sclerosing Cholangitis: A Focus on Secondary Causes," *Hepatology* 44, no. 5 (2006): 1063–1074.

19. E. J. Heffernan, T. Geoghegan, P. L. Munk, S. G. Ho, and A. C. Harris, "Recurrent Pyogenic Cholangitis: From Imaging to Intervention," *American Journal of Roentgenology* 192, no. 1 (2009): W28–W35.

20. J. Menon, A. Rammohan, M. Vij, N. Shanmugam, and M. Rela, "Current Perspectives on the Role of Liver Transplantation for Langerhans Cell Histiocytosis: A Narrative Review," *World Journal of Gastroenterology* 28, no. 30 (2022): 4044–4052.

21. Y. Tang, Z. Zhang, M. Chen, et al., "Severe Sclerosing Cholangitis After Langerhans Cell Histiocytosis Treated by Liver Transplantation: An Adult Case Report," *Medicine* 96, no. 9 (2017): e5994.

22. V. Kamalumpundi, J. Rieth, H. Tran, M. Ashat, and X. Zhang, "A Case of Erdheim-Chester Disease Causing Secondary Sclerosing Cholangitis," *ACG Case Report Journal* 10, no. 1 (2023): e00963.