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Long-term outcomes of biliary atresia patients surviving with their native livers

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ABSTRACT

Portoenterostomy (PE) has remained as the generally accepted first line surgical treatment for biliary atresia (BA) for over 50 years. Currently, close to half of BA patients survive beyond 10 years with their native livers, and most of them reach adulthood without liver transplantation (LT). Despite normalization of serum bilirubin by PE, ductular reaction and portal fibrosis persist in the native liver. The chronic cholangiopathy progresses to cirrhosis, complications of portal hypertension, recurrent cholangitis or hepatobiliary tumors necessitating LT later in life. Other common related health problems include impaired bone health, neuromotor development and quality of life. Only few high-quality trials are available for evidence-based guidance of post-PE adjuvant medical therapy or management of the disease complications. Better understanding of the pathophysiological mechanisms connecting native liver injury to clinical outcomes is critical for development of accurate follow-up tools and novel therapies designed to improve native liver function and survival.

1. Introduction

Biliary atresia (BA) is a cholangiopathy of unclear etiology and pathophysiology diagnosed only among newborns, representing the most common indication for liver transplantation (LT) in childhood [1]. The fibro-inflammatory destruction of the extrahepatic and intrahepatic bile ducts results in cholestatic liver injury and rapidly progressing biliary cirrhosis [1,2]. The first line surgical attempt to prevent disease progression by restoring bile flow involves portoenterostomy (PE), wherein the destructed extrahepatic biliary tree is replaced with a jejunal conduit. A successful PE (SPE), marked by normalization of serum bilirubin, also referred as clearance of jaundice (COJ), enables long-term survival with native liver (NL) [2]. Currently, nearly half of all BA patients undergoing PE survive for at least 10 years with their native livers and over one-quarter reach adulthood without LT in Europe [3–7]. Despite SPE, the NL disease continues as variably progressing chronic cholangiopathy characterized by advancing liver fibrosis underpinned by marked bile ductular proliferation, also known as ductular reaction [8–10]. The underlying risk factors and mechanisms of the progressive liver injury remain unclear, although early surgery before the age of two months seems to provide the best chance for long-term native liver survival (NLS) [3]. Clinical sequelae of the chronic liver disease among long-term NL survivors include cirrhosis, cholangitis, portal hypertension (PH), recurrent cholestasis, synthetic liver failure and liver tumors (**Figure**), which also represent the leading indications for LT in adolescence and adulthood [11–13]. Other common health issues include impaired bone health, neurodevelopmental impairments, and reduced quality of life (**Table**). Detailed understanding of progression of the chronic cholangiopathy and its complications among NL survivors is vital for optimal patient management and follow-up including timing of LT. Our aim is to address outcomes of BA patients surviving with their native livers, whereas post-LT outcomes are beyond the scope of this review. (see Table 1, Fig. 1)

1.1. Portoenterostomy and native liver survival

1.1.1. Successful portoenterostomy enables long-term native liver survival

Aspired short-term outcome of PE entails normalization of serum

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bilirubin level, reflecting successful restoration of adequate bile flow from the liver to the intestine, a discernible prerequisite for long-term NLS [2]. In a Nordic multicenter study of 148 patients, only 10% of the patients who failed to reach serum bilirubin below 20 μmol/l following PE survived with NL for 2 years, as opposed to over 90% 2-year NLS among those who normalized their serum bilirubin [5]. The positive effect of bilirubin normalization on NLS only increased with longer follow-up. The respective NLS rates were 83% and 4.3% at 5 years and 75% and 0% at 10 years among those who normalized bilirubin compared to those whose post-PE bilirubin remained above 20 μmol/l [5]. A nationwide Dutch study reported that nearly 80% of 100 2-year NL survivors had reached serum bilirubin <20 μmol/l within 6 postoperative months [14]. In both studies normalization of serum bilirubin was the single most powerful predictor of extended NLS [5,14]. In tune with these findings, 82% of North American BA infants with serum bilirubin <34 μmol/l (2 mg/dl) by 3 months were alive with NL at age 2 years, as opposed to only 22% with bilirubin ≥34 μmol/l [15].

Whilst true long-term NLS is exceptional, if possible, without COJ after PE, pathophysiologic counterparts for this observation have been rarely addressed. Interestingly, rapid postoperative decline of serum bilirubin to very low levels below the upper limit of normal associates with decreased progression of liver fibrosis and very high NLS rate approaching 100% by 10 years [16]. Among NL survivors with stable or decreasing liver fibrosis between biopsies obtained at PE and median age 4.4 years, serum bilirubin had normalized in 0.65 months–5.5 μmol/l at 3 months after PE, the figures being much lower what is traditionally regarded as limits for SPE [16]. These findings highlight the link between efficient resolution of cholestasis for prevention of progressive liver fibrosis, offering therapeutic target for prolonging long-term NLS.

1.1.2. *Long-term native liver survival rates*

In the largest and most recent European series NLS was 41–55% at 5 years and 35–47% at 10 years after PE, which was performed in over 93% of all BA cases in each study cohort [3–6]. Documented post-PE serum bilirubin normalization (≤20 μmol/l) rate ranged between 36% and 64% [3–6]. In French and Dutch national studies with extended follow-up, 26% and 27% of patients survived with NL for at least 20 years [3,7]. In the largest European cohort from France comprising 1340 post-PE patients, 20-year NLS remained unchanged at 26% between

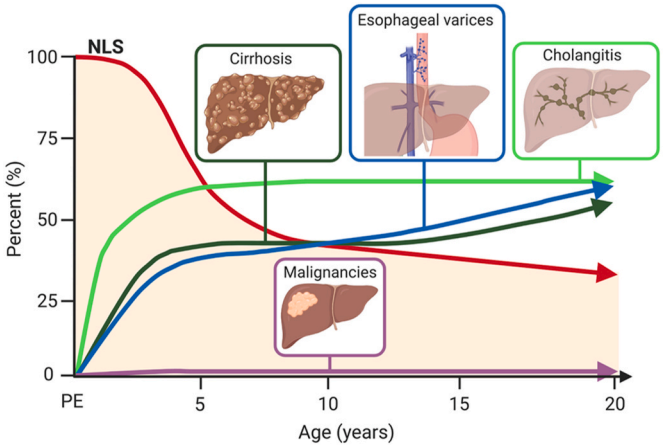

Fig. 1. Cumulative proportional occurrence of cirrhosis, esophageal varices, cholangitis and liver malignancies in relation native liver survival (NLS) from portoenterostomy (PE) to adulthood (Created with BioRender.com).

different eras during 1986–2015 [3], whereas in the Dutch study of 104 patients 20-year NLS improved from 20% to 33% among patients operated during 1977–1982 and 1983–1988, respectively [7]. The Japanese Biliary Atresia Registry reported 49% 20-year NLS among 3160 patients operated during 1989–2015 [17]. In both French and Japanese cohorts, younger age at PE associated with significantly improved long-term NLS [3,18]. PE age less than 60 days also associated with a higher frequency of COJ in the Japanese cohort, providing further support for the advantage of early PE [18]. In both French and Japanese national cohorts, the NLS advantage of early PE was most marked in the age group ≤30 days, showing approximately 15–20% higher NLS at 15–20 years when compared to those operated after age 60 days [3,18]. Long-term NLS curves of infants operated between 30 and 60 days of life settled between the two age extremities [3,18].

The observation that early PE improves NLS has been increasingly exploited for therapeutic purposes. Several countries and institutions have implemented screening programs for timely diagnosis of BA to enable earlier surgical intervention. Most screening programs have employed stool color card thus far and promising results has been

Table 1
Long-term health issues for biliary atresia patients alive with native livers.

	Infancy	Childhood	Adulthood	Implications for surveillance and care
Growth	Prior to COJ, both height and weight gain are impaired	In nonjaundiced patients, stable growth	Majority reach normal adult height and weight	Regular assessments of growth, schedule adapted according to age-group's growth pace Optimization of nutrition with energy-supplementation in infancy
Bone Health	In cholestasis, increased risk for rickets and fractures	Insufficient nutritional vitamin D intake may predispose to fractures	Insufficient nutritional vitamin D intake may predispose to impaired bone density and fractures Risk of osteopenia and osteoporosis in advanced state of liver insufficiency	Low threshold for investigation of low-energy fractures for cholestatic patients In advancing liver disease, regular surveillance of bone mineral density Surveillance of serum vitamin D-levels and adequate individual supplementation of vitamin D as well as calcium, when needed
Neurodevelopment	Native liver survivors: slight deviation from norms at 1 and 2 years of age	In Northern American population neurocognitive function comparable to norms European studies suggest impaired intelligence quotient and impaired motor skills	No difference in educational levels or employment rates compared to norm population	Structured developmental assessment to detect patients with motor or neurocognitive impairments
Health-related quality of life	Parents experience elevated stress	In European and Asian populations, HRQoL does not differ from healthy controls or LT patients In Northern American population, decreased HRQoL compared to norm population	In European populations, HrQoL experienced by young adults comparable to background population	Psychological support for parents at early stage of diagnosis and later on, when needed Psychological as well as social services support for patients when needed

COJ: clearance of jaundice; HRQoL: health-related quality of life; LT; liver transplantation.

recently reported by measuring serum conjugated or direct bilirubin in newborns [19,20]. Experiences from several screening programs have confirmed the advantages of early surgery, resulting in more frequent normalization of serum bilirubin and improved NLS [19,20].

1.2. Chronic liver disease in native liver survivors (Figure)

1.2.1. Mechanisms of native liver injury after successful portoenterostomy

SPE elicits advantageous changes to liver histopathology by relieving cholestasis and resolving the neutrophil-dominated acute inflammation [8]. Unfortunately, the NL disease still progresses as chronic cholangiopathy, characterized by persistent ductular reaction and increasing portal fibrosis eventually leading to cirrhosis [9,10]. On cellular level, ductular reaction and fibrosis following SPE are evident as neo-bile duct forming cholangiocytes and proliferation of extracellular matrix (ECM) producing myofibroblasts [8].

Recently, mRNA sequencing was utilized to assess the relative cellular abundancies among NL survivors [21]. This study, analyzing liver biopsies from 8 NL survivors obtained 1 year after SPE and comparing them to biopsy data acquired at PE, confirmed the attenuation of acute inflammation as evident by decreasing neutrophils and tissue monocytes (macrophages and Kupffer cells). In addition, persistent ductular reaction and portal fibrosis were evident as increasing relative abundancies of cholangiocytes and activated portal fibroblasts (aPF) [21]. The increasing cholangiocyte and aPF abundancies are of interest as cholangiocytes have been suggested to promote BA fibrosis by activation of aPFs [22–25]. In accordance with previous clinical and histopathological studies, SPE was leading to attenuation of inflammatory pathways with a concomitant progression of fibrosis as evident by the emergence of an ECM related molecular fingerprint [21]. The ECM related genes markedly differed between PE and post-SPE samples suggesting the post-SPE cholangiopathy to be a dynamic process involving significant changes in the molecular activity of ECM environment [26]. Based on this data, it is tempting to speculate that ECM related molecules may actively promote the fibrotic process during post-SPE cholangiopathy [27].

Studies assessing the molecular landscape of post-SPE NL injury are scarce [1]. A study by Kerola et al., analyzed the potential role of matrix metalloproteinase-7 (MMP-7) in post-SPE cholangiopathy [28]. In the analysis of liver biopsies from 25 NL survivors on average 3 years after PE, the liver expression and serum concentration of MMP-7 associated with the liver fibrosis stage. In addition, the increased MMP-7 expression localized in ductular reaction regions with a similar expression pattern to cholangiocyte marker cytokeratin-7. Subsequent studies have confirmed the potential of MMP-7 both as a biomarker and a promoter of cholangiopathy in BA mouse model [29].

1.2.2. Cholangitis

Cholangitis is a frequent and serious complication after PE, occurring most likely as an ascending infection via intestinal Roux loop although hematogenous or lymphatic spread are also possible mechanisms [30–32]. Postoperative cholangitis affects about two thirds of the patients regardless of the use of prophylactic antibiotics [16,31,33,34]. High GGT levels, older age, and impaired nutritional status at PE have been reported to associate with increased risk of cholangitis episodes [35–37]. Development of hepatic bile lakes promotes biliary stasis and is another important risk factor for recurrent cholangitis after PE [38].

Cholangitis frequency is highest during the first months and years after PE, and patients experiencing cholangitis during this time period are also at highest risk for recurrent episodes [31,35]. Although the risk of cholangitis is greater if COJ is not achieved [31], about two thirds of NL survivors have had at least one cholangitis episode by the age of 10 and one third of them still experience cholangitis in the adult age [34,39,40]. Repeated cholangitis during the first years post-PE decreases NLS regardless of COJ status [33,35,38]. In one center, all patients experiencing cholangitis within three months of PE required early LT despite initial COJ [36]. However, occurrence of late cholangitis also negatively affects prognosis, as NL survivors experiencing cholangitis during adolescence are at increased risk for LT in young adulthood [13].

Febrile cholangitis should be treated with intravenous antibiotics, and blood cultures should always be collected [31,32]. Positive blood cultures or high bilirubin levels may be risk factors for poor treatment response [31]. Ultrasound and/or MRCP should be performed particularly in case of repeated cholangitis, as bile lakes can be found in up to one quarter of patients with recurrent cholangitis [38]. Operative drainage of bile lakes both reduces cholangitis frequency and improves NLS [38].

1.2.3. Portal hypertension

PH develops invariably after an unsuccessful PE but is common also after COJ. Defining PH based on occurrence of its complications likely underestimates its frequency as portal pressure is elevated before complications develop [41]. PH - defined as either the presence of esophageal varices or both splenomegaly and thrombocytopenia - affects over half of COJ patients by the age of one year and two thirds by the age of nine years [41,42]. Studies among patients surviving with their NL until adulthood report PH in 50–95% of patients, however, without clearly defined diagnostic criteria [7,39,43]. Development of PH parallels the progression of histological liver fibrosis and associated with an increased risk for LT [13,42]. In addition to progressive liver fibrosis, obliterative portal venopathy and intrahepatic hemodynamic changes leading to decreased portal supply to the detriment of increased arterial supply for proliferating bile ductules may contribute to the high PH susceptibility among NL survivors [44,45].

Esophageal varices eventually develop to all BA patients with PH [42]. The mortality rate for variceal bleeding in children may be as high as 8%, while the incidence of life-threatening spontaneous bleeding episodes approaches 20% among children with cirrhosis [46,47]. Primary prophylaxis of variceal bleeding by sclerotherapy or variceal ligation is efficient particularly among BA patients whose bilirubin has normalized after PE, whereas after failed PE varices appear at younger age, bleed more often, and recur earlier after eradication [48]. After COJ, bleeding episodes may be virtually completely prevented by routine endoscopic surveillance and variceal eradication [48,49]. On the other hand, when primary prophylaxis is not systematically applied, bleeding has been reported to occur in 9–20% of COJ patients by the age of 9 years [34,41] and in up to 30% of those surviving with their NL until adulthood [7,39,40]. In addition to generally accepted secondary prophylaxis following variceal bleeding [50], many pediatric centers currently follow adult practice of endoscopic primary prophylaxis of variceal bleeding in BA [47,48]. In selected patients with low bilirubin levels and preserved liver synthetic function, portosystemic shunt surgery may be considered to alleviate severe PH symptoms such as recurrent bleeding [19,51]. Due to hypoplastic intrahepatic portal veins and frequently small patient size, transjugular intrahepatic portosystemic shunts are less likely to be successful in BA patients but can occasionally serve as a bridge for LT [51].

Other, less frequent complications of PH include ascites, hepatopulmonary syndrome (HPS), and portopulmonary hypertension (PPH) [43]. Ascites can be observed in less than 10% of patients, most of whom present with thrombocytopenia and splenomegaly [34,41]. HPS, caused by intrapulmonary vascular dilatations or portosystemic shunts, is more common of the pulmonary manifestations of PH, described in 5% of pediatric NL survivors and affecting up to 20% of children listed for LT [41,43]. HPS usually affects younger children, while PPH is typically detected in adolescents and more often in females [52]. PPH is often asymptomatic at diagnosis but later causes dyspnea, hypoxia, and eventually right-sided heart failure caused by increased pulmonary artery pressure [43,52]. PPH is rare, affecting $<1\%$ of children with end-stage liver disease [43]. In both HPS and PPH, arterial blood gas determination shows hypoxia whereas pulse oximetry findings are abnormal only in HPS and blood saturation may be normal in PPH [43,

52]. The diagnosis of HPS is based on saline contrast-enhanced echocardiography and macroaggregated albumin lung perfusion scan demonstrating an increased right-to-left shunting [43]. Echocardiography findings may even be relatively normal in PPH, the diagnosis of which requires cardiac catherization to measure pulmonary artery pressure and resistance [52]. Pulmonary manifestations of PH indicate listing for LT before severe cardiac complications develop and contraindicate transplantation [43,52].

1.2.4. Liver tumors

Development of cirrhosis predisposes BA patients to hepatocellular carcinoma (HCC), which has been described in approximately 1% of patients and can be detected already in infancy [53,54]. The majority of HCC in BA have been described in children younger than 10 years of age, and about half of the cases have been incidental findings in the explanted liver at time of LT [53–55]. In addition, cholangiocarcinoma and hepatoblastoma have been reported, while benign tumors such as focal nodular and regenerative hyperplasia and adenoma are relatively common findings [7,52]. Since HCC usually associates with elevated serum alpha fetoprotein levels, monitoring alpha fetoprotein together with abdominal ultrasound at 6–12 month intervals is recommended after PE in order to detect hepatic lesions in their early stage [54,55]. Discrimination of HCC from regenerative liver nodules may be challenging or even impossible in case of AFP-negative disease [55]. Prompt evaluation for LT is crucial when HCC in suspected in BA patients [55].

1.3. Long-term health of native liver survivors (Table)

1.3.1. Growth

In early infancy, due to on-going cholestasis and elevated energy requirements, both the height and weight gain of BA patients are impaired [56,57]. Active surveillance and promotion of adequate nutritional status is essential for optimal LT outcomes. After resolution of jaundice, growth impairments amend between 12 and 18 months of age [56,57]. Studies evaluating the growth of long-term NL survivors between ages 5–24 years have depicted normal height and weight for the vast majority of patients [34,58,59]. A French cohort with 63 patients who survived at least until 20 years of age with NL reported 78% of patients had an adult height at or above mean [39].

1.3.2. Bone health

Although deficiency in vitamin A, E and K is relatively uncommon after COJ and mainly affects those whose bilirubin levels remain elevated [60], vitamin D deficiency affects the majority of patients at PE and insufficiency may persist up to one year after a successful PE despite enteral supplementation [61,62]. In addition to depletion of intestinal bile acids, another possible mechanism predisposing to low vitamin D levels in BA is poor hepatic 25-hydroxylation [61]. Low levels of vitamin D predispose to rickets as well as osteoporosis, which may develop even after a successful PE [62–64]. Other predisposing factors include chronic inflammation, malnutrition and low calcium and phosphorus intake. The incidence of bone fractures was found to be as high as 15% in a sample of NL survivors who had normalized their bilirubin but were not on routine vitamin D supplementation [34]. The risk of bone disease further increases with development of cirrhosis and end-stage liver disease; up to one third of pediatric LT recipients have experienced fractures, most of which are located in the thoracic spine [65]. The majority of vertebral fractures have been reported to be asymptomatic, which underlines the need for bone mineral density surveillance especially for patients with advanced state of liver disease [62,66]. Since the commonly used enteral vitamin D supplementation of 400 IU may be insufficient [61], all BA children should undergo regular monitoring of vitamin D levels according to which the supplementation, intramuscularly when needed, is defined [60].

1.3.3. Neurodevelopment

Childhood cholestatic disease predisposes to PH, malnutrition, infections, and hepatic encephalopathy, all of which may negatively influence neurodevelopment [67]. At infancy, BA patients surviving with their NL demonstrate impairments in language and motor skills [68]. Unsuccessful PE, ascites, and poor growth were identified as predictors of developmental delays, however, as many as 25–50% of children having undergone a successful PE were also at risk for decreased neurodevelopmental outcomes [68]. Among older children, too, signs of advanced liver disease including elevated bilirubin and PH predict lower intelligence scores [67]. Although most North-American NL survivors aged 3–12 years presented with normal neurodevelopment [67], decreased intelligence quotient and impaired motors skills were similarly found in two recent national studies from Europe [69,70]. Adult NL survivors demonstrate normal development as well as educational levels and employment rates comparable to general population [7,40,71,72]. It appears that younger BA children with worst neurodevelopmental results end up in earlier LT [67]. Unfortunately, children transplanted in young age continue to underperform in cognitive tests several years after their LT, suggesting the neurodevelopmental impairment occurring in early infancy may be persistent [73]. Careful health monitoring and optimal LT circumstances of the NL survivors who approach end-stage liver disease are crucial [73].

1.3.4. Quality of life

Health-related quality of life (HRQoL) outcomes among BA are variable. In a large North American sample, HRQoL was significantly reduced among BA NL survivors when compared to healthy children, similar to pediatric LT recipients [74]. Instead, apart from lower school functioning scores caused by hospital visits during school days, Finnish NL survivors reported HRQoL scores comparable to healthy controls [75]. Similarly, in a Malaysian sample of school-aged children, HRQoL scores were comparable between BA NL survivors, LT recipients, children with other chronic liver diseases, and healthy controls [76]. Dutch and Italian samples among young adults also reported the HRQoL outcomes of nontransplanted BA patients comparable to healthy controls, although general health perception was decreased among Italian BA females [77,78]. Since parental stress may be extreme among BA patients' families and contributes to children's perception of health and adaptation to illness [75], medical care providers should pay attention to family support. Overall, most NL survivors appear to have a HRQoL comparable to healthy subjects.

1.4. Therapeutic approaches to prolong native liver survival

1.4.1. Steroids

Adjuvant therapy with short courses of high-dose steroids during the immediate postoperative period have associated with improved COJ rates [79–84], a finding supported a meta-analysis [83]. However, randomized controlled trials (RCT) have not found the use of steroids to associate with improved COJ rates [85,86], and none of the randomized or prospective trials could demonstrate any benefit of steroids regarding NLS [82,85,86]. No increased complication rates related with steroid use have been reported, although in one RCT trial complications occurred earlier in the steroid than placebo group [86]. However, high-dose corticosteroid therapy has been shown to have a short-term negative effect on BA patients' height gain, without influence on final growth [57,87]. Despite deficient evidence, since improved COJ rates without significantly increasing complications have been obtained, over half of European centers reported use of a steroid-based postoperative regimen [88].

1.4.2. Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) is a hydrophilic secondary bile acid, which promotes bile flow by upregulating canalicular and basolateral export pumps as well as protects hepatocytes from bile acid toxicity by

diluting the pool of toxic bile acids [89]. Although evidence is limited, UDCA >15 mg/kg/day is widely used after PE in the Western world [5,88]. In combination with steroids, a small dose of UDCA (10 mg/kg/day) has been reported to associate with improved COJ rates [79] and UDCA 20 mg/kg/day even with improved short-term NLS [80]. The positive effect on COJ was confirmed in a recent meta-analysis [81]. The effects of UDCA alone have been studied both after SPE [90] as well as in a sample where the majority remained jaundiced after PE [91]. After COJ, cessation of UDCA 25 mg/kg/day resulted in worsening of liver biochemistry which improved after reintroduction of medication [90]. In contrast, UDCA was ineffective in a sample where the majority had undergone an unsuccessful PE [91]. These results suggest UDCA may be beneficial after COJ by improving liver biochemistry among NL survivors.

1.4.3. Antibiotics

There is no consensus whether prophylactic antibiotics to prevent cholangitis should be administered after PE, however, their routine use, mostly sulfamethoxazole/trimethoprim, was reported by two thirds of European centers [88]. In a systematic review, only four eligible studies were found, and the benefits of antibiotics could not be confirmed based on their results [92]. Interestingly, in a Dutch national sample, use of prophylactic antibiotics was independently associated with improved long-term NLS [6]. One RCT reported lower recurrence rates among patients who were administered prophylactic antibiotics after their first cholangitis episode compared to those who received no antibiotics [93]. Considering that particularly early and recurrent cholangitis episodes increase the risk of LT [33,35,38,94], robust clinical trials addressing effectiveness of antibiotics are needed.

1.4.4. Emerging adjuvant therapies

There is an urgent need for efficient adjuvant therapies for post-PE cholangiopathy to extend NL survival. Of the novel medical agents used for a variety of adult liver diseases, farnesoid X receptor (FXR) agonists, fibroblast growth factor-19 analogs, and apical sodium dependent bile acid transporter (ASBT) inhibitors are emerging to be tested also for treatment of BA [95]. Their ability to reduce hepatic synthesis or intestinal re-absorption of bile acids may alleviate liver injury and pruritus by reducing harmful accumulation of bile acids into hepatocytes and systemic circulation [96]. *Nor*UDCA is a side chain shortened UDCA derivative which protects the biliary epithelium and hepatocytes from the toxic effects of bile acids and improves cholestasis in sclerosing cholangitis [97], suggesting it could be beneficial also in BA. Although early experiences from pilot clinical studies are optimistic [98], completion of ongoing phase 2 trials with FXR agonists and ASBT inhibitors will provide more robust evidence on their efficacy in BA [95,96].

1.4.5. Summary

For more than 50 years PE has remained as the first line surgical treatment of BA. Although nearly half of the patients survive with NL for over 10 years, most of them are affected by sequelae of the persisting chronic cholangiopathy, including cirrhosis, PH, cholangitis and liver tumors, necessitating life-long follow-up [99]. While the long-term complications of NL disease are well characterized among children and adolescents, their occurrence in adulthood, underlying pathophysiology and the mechanisms of progressive NL injury remain unclear. In addition to liver complications, NL survivors are predisposed to impaired bone health, neurodevelopmental problems and reduced quality of life, which should be taken into account during follow-up. Only few high-quality clinical trials have been performed for evidence-based guidance of post-PE adjuvant medical therapy or management of the disease complications. Deeper insight into the pathophysiological mechanisms connecting the progressive NL injury to clinical outcomes is critical for development of accurate follow-up tools and novel therapies designed to improve survival with NL.

1.5. Practice points

- Following PE, nearly half of BA patients survive beyond 10 years with their native livers, and most of them reach adulthood without LT
- The chronic cholangiopathy leads to cirrhosis and complications of PH in most long-term NL survivors and associates with recurrent cholangitis and occasional liver malignancies
- Impaired bone health, neurodevelopmental impairments, and reduced quality of life are other common health concerns
- NL survivors require life-long special follow-up for optimal management of complications and timing of LT

1.6. Research agenda

- Underlying mechanisms of the progressive NL injury in relation to clinical disease complications and their pathophysiology should be clarified
- High-quality clinical trials are required for evidence-based clinical management of esophageal varices, cholangitis and other NL disease complications
- Innovative future research is needed to develop efficient medical therapies to prevent progression of NL injury and to prolong NLS

Declaration of competing interest

None.

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