Referral Patterns, Co-occurring Conditions and Survival Outcomes of Biliary Atresia in Thailand: A Data Mining Study from the National Health Security Office Registry

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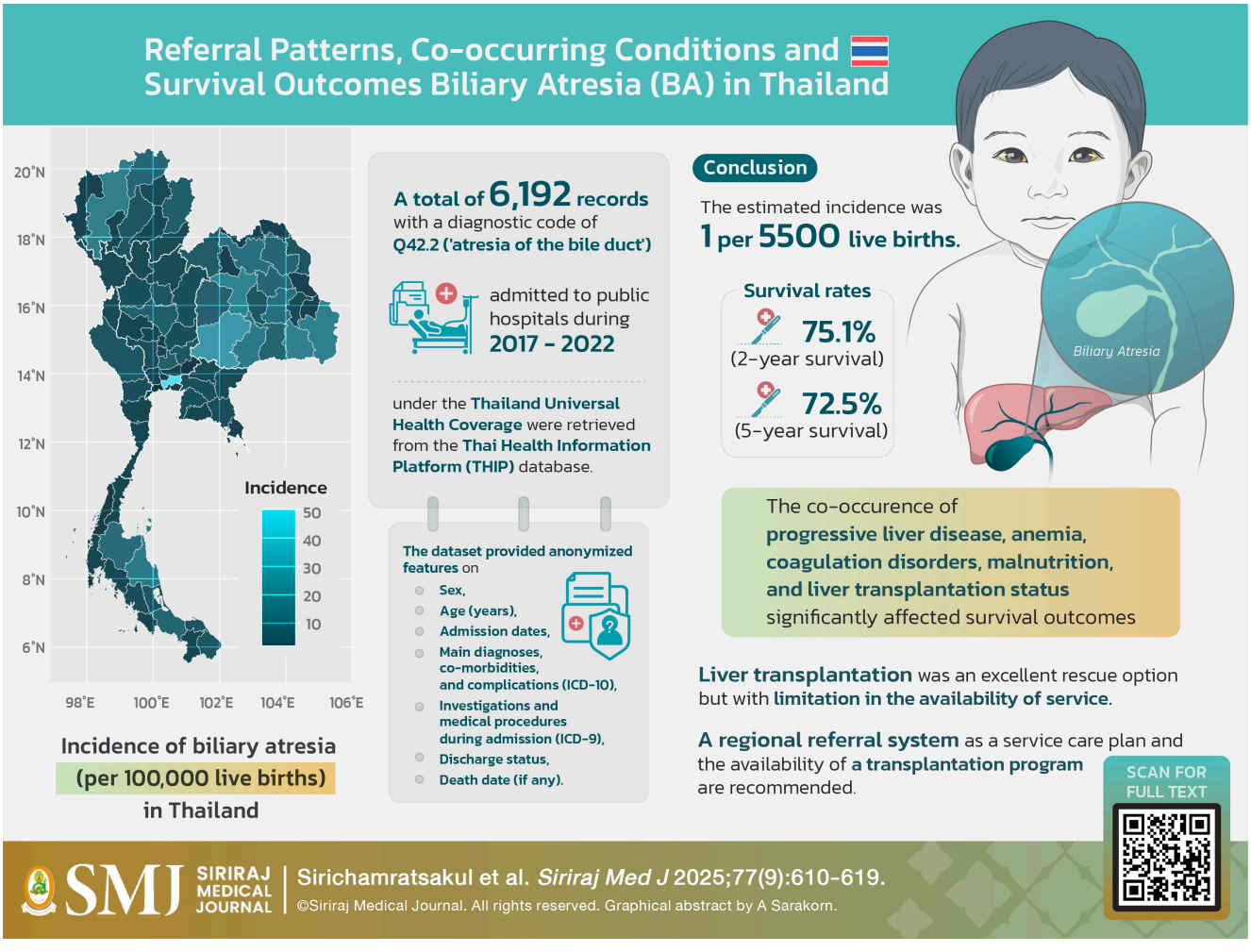

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Received 27 November 2024 Revised 11 January 2025 Accepted 14 January 2025
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https://doi.org/10.33192/smj.v77i9.272428

ABSTRACT

Objective: This study aimed to identify comorbidities and referral patterns in biliary atresia (BA) patients and analyze their influence on survival outcomes using a large national reimbursement cohort.

Materials and Methods: Data were extracted from the National Health Security Office (NHSO) registry via the Thai Health Information Portal (THIP). Patients under six years with a diagnosis of BA between 2017 and 2022 were included. Comorbidities, referral patterns, and survival were analyzed; association rule analysis was performed using the mlxtend package in Python 3.9, whereas survival analysis was conducted using the Kaplan-Meier survival curve.

Results: In total, 957 BA cases among 4,168 admissions were included. The estimated annual incidence was 108.7 cases (1.8 per 10,000 live births). The 2- and 5-year survival rates were 75.1% and 72.5%, respectively. Association rules analysis revealed that metabolic disorders, liver cirrhosis, and portal hypertension had a high confidence of co-occurrence with BA. Anemia, coagulation disorders, malnutrition, liver cirrhosis, hepatic failure, ascites, and hypoalbuminemia were significantly associated with poorer survival outcomes. Cases with more than one referral before a definitive surgery significantly had poorer survival outcomes.

Conclusion: Overall, BA patients in Thailand had fair survival rates. Co-occurring progressive liver diseases, anemia, coagulation disorders, malnutrition, and prolonged referrals significantly contribute to poorer survival. Managing these peri-operative factors might improve the outcome of this devastating disease.

Keywords: Biliary atresia; children; infants; survival; Thailand (Siriraj Med J 2025; 77: 610-619)

INTRODUCTION

Biliary atresia (BA) is a rare yet significant condition that may lead to liver failure and mortality in infants.[1] Its incidence varies across the globe, affecting 1 in 14,000–20,000 live births in Europe and 1 in 16,000–20,000 live births in Canada and the USA.[2] In East Asian countries, BA is more prevalent, affecting around 1 in 5,000–9,600 live births.[3] The etiology of BA remains unclear. However, its mainstay pathology is progressive severe sclerosing inflammation of the bile ducts at the porta hepatis, leading to periportal fibrosis, complete biliary obstruction at the hepatic outflow, and biliary cirrhosis. Surgical restoration of bile flow by a Kasai hepatoportoenterostomy (KPE) is the current standard intervention, with liver transplantation (OLT) considered in cases of late presentation or severe decompensation of liver functions.[4,5]

Approximately half of BA patients survive ten years post-KPE with their native liver.[6] Immediate bile flow restoration following KPE is the most influencing determinant of survival in BA patients. Reported biliary drainage after KPE was around 50-60% of cases.[7,8] However, even in the cases that achieved good biliary drainage, inflammation, and cirrhosis might slowly progress with a consequence such as portal hypertension, malnutrition, failure to thrive, and death.[9] Surveillance and proper management of comorbidities are of primarily important in the postoperative period. Considering surgical quality improvement purposes, a multi-institutional registry should be conducted for a rare disease like BA and other rare congenital anomalies. In Thailand, almost all cases suspected of BA were referred for definitive treatment at a tertiary-level public hospital. There is currently no successful registry at the national level for BA in the country, and the dataset that might be the nearest to the population level is the reimbursement registry of the National Health Security Office Registry (NHSO) data. The dataset includes all admissions in the country, spanning the 6-year period from 2017-2022, with accurate survival status. This analysis used data mining tools to analyze the incidence, co-occurring diagnosis, referral patterns, and survival outcomes of BA cases in Thailand. In addition, associations between co-morbidities and survival were analyzed.

MATERIALS AND METHODS

This retrospective cohort study utilized data mining techniques on data extracted from the reimbursement data repository of the NHSO through the Thai Health Information Platform (THIP), with permission from the local ethics committee (Human Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University, REC.66-529-10-1).

Data source

A total of 6,192 records with a diagnostic code of Q42.2 ('atresia of the bile duct') admitted to public hospitals under the Thailand Universal Health Coverage (UHC) scheme were retrieved from the database. THIP was a joint project between the Institute of Research and Development for Health of Southern Thailand and

the National Science and Technology Development Agency (NSTDA) that archived reimbursement data from the NHSO.[10] When filtering with the patients' age equal to or less than six years, 957 unique cases (4,168 admissions) were included for analysis. The dataset provided anonymized features on sex, age (years), admission dates, main diagnoses, co-morbidities, and complications (ICD-10), investigations and medical procedures during admission (ICD-9), discharge status, and death date (if any). To estimate a population-based incidence rate, we obtained mid-year population data on live births in each district from 2017 to 2022 from the Bureau of Registration Administration, Department of Provincial Administration, Thailand.

Geographical distribution analysis

Geographical distribution was assessed by calculating the average incidence per thousand live births in each district based on each year's average observed incidence and live birth population. Thailand is divided into 76 provinces and 878 administrative districts, with the population of the districts varying from 1,991 to 260,565 and an average population of 50,000. To address the standardized incidence rate, smaller districts were combined with larger ones to form a standardized district (SD), averaging 150,000 people, following Babcock's approach. The baseline district population of the year 2017 was used to account for changes over the study period.

Association rule analysis

To discover the co-occurrence conditions in BA, the Apriori model was used as a data mining algorithm.[11,12] The algorithm uncovers co-occurring diagnoses or complications with the defined diagnosis in terms of the association rule and calculates the likelihood that a condition will be diagnosed given that another item has already been diagnosed and reports as 'confidence'. The analysis used BA (ICD-10 'Q42.2') as the preceding and calculated the 'confidence', 'support', and 'lift' of the co-occurrent conditions. Analysis used the 'association_rules' and the 'apriori' modules of the mlxtend package on Python version 3.9. The threshold used for filtering was a minimum support of 0.05, confidence of at least 0.6, leverage of at least 0, and a lift of at least 1.0.

All co-occurrences were analyzed with survival data using the lifelines package. The p-value threshold for survival analysis was adjusted by the number of all occurrences tested (1,057) by Bonferroni's correction method to be 0.00005 ($5x10^{-5}$). The Manhattan plot was performed with the altair package on Python. The Kaplan-Meier survival curve was constructed on Stata version 14.0 (Stata, TX). All computational codes can be provided on request.

Referral pattern analysis

Cases who did not undergo a KPE (ICD-9 '51.37') on their first admission were regarded as referred cases. Referral duration was the time difference between the first admission when BA was diagnosed and/or the admission when KPE was performed. Survival was compared between cases that underwent an operation on their first admission and those that were referred.

RESULTS

In total, 957 unique cases with the code of BA were recorded among 4,168 admissions during the 6-year period. When filtered by the age criteria, the number of cases aged no more than six years was 750, with 3,349 admissions. The average number of unique cases per year in patients aged < 2 years, likely new cases, was 652, resulting in a crude incidence rate of 18 cases per 100,000 live births. The male-to-female sex ratio was 334:318 or 1.05. The estimated average age on the admission of the patients was 0.17 years or 2 months and the average weight was 3.34 kilograms (standard deviation 2.97). There was recorded mortality in 194 cases in the study period, giving a crude survival rate of 74.1%. When analyzed with a Kaplan-Meier survival estimation, the crude 2-year and 5-year survival rates were 75.1% and 72.5%, respectively.

Associated conditions in BA and their impact on survival

With the conditions described in the method section (support > 0.05, confidence > 0.6, association rule analysis by Apriori algorithm identified 38 significant co-occurrences. After filtering the duplications and unspecific conditions i.e. Fever (R50.9), 16 conditions remained, showing high-confidence associations between BA and metabolic disorders, esophageal varices, cholangitis, liver cirrhosis, and portal hypertension (Table 1). Pre-Kasai cirrhosis occurred in 15.6% of the patients, followed by portal hypertension, coagulation defects, and anemia. At the first admission, esophageal varices and cholangitis were observed in 1.2% and 7.8% of the patients, respectively. Malnutrition and vitamin and mineral deficiencies, particularly vitamin D, hypokalemia, and hyponatremia, were detected in approximately 4-9% of patients at the first admission. Among those with cirrhosis, 236 (67.4%) patients developed cirrhosis since their first admission before the KPE, whereas 101 (29.0%) developed cirrhosis after the KPE. Cholangitis, a major complication of the KPE, occurred in 6.7% of patients with BA at the

TABLE 1. Apriori association rules analysis; biliary atresia-associated conditions that have high support and confidence levels.

ICD-10	Clinical definition	Support	Confidence	Lift
K74.60	Cirrhosis	0.212	0.212	1
K83.0	Cholangitis	0.179	0.179	1
R18	Ascites	0.139	0.139	1
K76.6	Portal hypertension	0.122	0.122	1
E87.6	Hypokalemia	0.092	0.092	1
I85.9	Esophageal varices without bleeding	0.091	0.091	1
E87.1	Hyponatremia	0.084	0.084	1
K74.4	Secondary biliary cirrhosis	0.084	0.084	1
D64.9	Anemia	0.068	0.068	1
I98.2	Esophageal varices in diseases classified elsewhere	0.064	0.064	1
E55.9	Vitamin D deficiency	0.059	0.059	1
Z94.4	Liver transplantation status	0.056	0.056	1
D50.9	Iron deficiency anemia	0.055	0.055	1
D68.9	Coagulation defects	0.055	0.055	1
E44.0	Moderate protein calorie malnutrition	0.055	0.055	1
D62	Acute post-hemorrhagic anemia	0.054	0.054	1

admissions prior to KPE, and 7.1% of patients after the operation. On average, the episode of cholangitis was 2.9 per patient. Cytomegalovirus (CMV) infection was recorded in 8.7% of patients with BA.

On procedural analysis, intraoperative cholangiography (IOC), wedge liver biopsy, and percutaneous liver biopsy were performed primarily in 188 (19.6%), 166 (17.3%), and 101 (10.6%) cases, respectively. During the study period, 287 instances of KPE were recorded, accounting for 44.0% of the estimated number of new cases. Liver transplantation was performed in 109 patients (11.4%), with 76.1% undergoing primary transplants and 23.9% undergoing a transplant after KPE. Primary transplantation was performed in 7.6% of patients with primary cirrhosis of the native liver, which occurred in 24.7% of patients with BA.

Survival analysis by log-rank test was performed for all 1,057 co-occurring diagnoses in 750 cases. Two-year survival was 72.5% (68.9%-75.5%). Using a p-value cutoff at 5 x 10^{-5}, 35 items were considered to have a significant survival impact (Fig 1). Note that the E category (Endocrine, nutritional, and metabolic diseases), K category (Diseases of the digestive system), J category (Diseases of the respiratory system), and D category (anemia and coagulopathy groups) had the highest frequency among conditions with survival impact. Considering together with Apriori co-occurrence analysis, cirrhosis, coagulation defect, electrolyte imbalance (hyponatremia and hypokalemia), ascites, and status post liver transplantation had high support, which meant that they were found as co-occurrences in high incidence and also had significant survival impact (Table 2). Note that transplantation was a protective factor on survival (Hazard ratio 0.11, 95% Confidence interval 0.03-0.34).

Fig 1. Manhattan plot between the ICD-10 categories (Alphabet groups) and -log (p-value) of the log-rank test for significant survival impact.

TABLE 2. Survival probability and Cox's proportional hazard ratio of frequent co-occurrence that significantly had survival impact.

ICD-10	Clinical definition	2-year survival (95% CI)	Hazard ratio (95% CI)
K74.6	Cirrhosis	58.9% (52.9%-64.5%)	2.42 (1.82-3.21)
R18	Ascites	51.8% (41.6%-61.1%)	2.16 (1.57-2.98)
E87.1	Hyponatremia	56.1% (48.5%-63.0%)	2.15 (1.62-2.85)
E87.6	Hypokalemia	54.5% (47.4%-61.1%)	2.51 (1.91-3.32)
E88.0	Hypoalbuminemia	51.7% (42.6%-60.1%)	2.13 (1.57-2.88)
Z94.4	Transplantation status	100% (NA)	0.11 (0.03-0.34)

95% CI: 95% confidence interval, NA: not calculated

Geographical disparities and referrals

At the standardized district (SD) level, Bangkok (BKK), the capital city, had the highest proportion of primary admissions for BA, accounting for 28.7% of the cases, followed by Songkhla (11.3%) and Chiangmai (8.6%) (Fig 2). Annual data revealed that the year 2017 had the highest admission number among the 6-year study period (182, 27.9%), followed by 2018 and 2021 (118, 18.1% and 95, 14.6%, respectively), reflecting the impact of coronavirus disease (COVID-19) pandemic.

When analyzed by health region (HR), the highest number of admissions occurred in HR-13 (Bangkok, 28.7%), followed by HR-12 (Songkhla,11.3%) and HR-1 (Chiang Mai, 8.6%). Within specific SD, the most frequent admissions were in SD-28 (Phaya Thai-Ratchathewi, 14.6%), SD-27 (Bangkok Noi, Bang Plad, 7.5%), and SD-153 (Muang Khon Kaen, 6.1%). Overall, BKK remained the most frequent place of hospitalization for BA, followed by Khon Kaen, Songkhla, and Chiang Mai (Fig 2).

Of the 1,023 referred admissions, patients who were

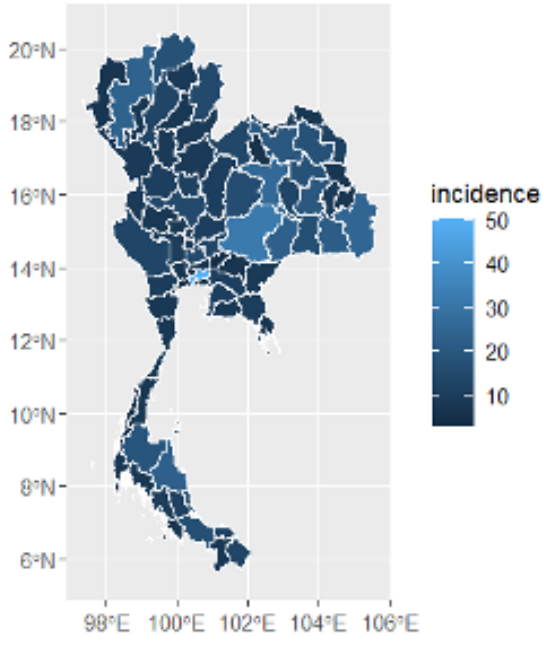

Fig 2. Incidence of biliary atresia (per 100,000 live births) in Thailand, categorized by province of first admission.

primarily admitted to BKK hospitals mostly remained within the BKK referral network (SD-24, SD-27, and SD-28), followed by referrals to SD-153 (Muang Khon Kaen) and SD-242 (Phitsanulok). The average number of visits in each individual patient was 4 (1-36); 5 patients had more than 10 visits, and 3 had more than 30 visits. These three patients with BA underwent KPE and subsequently developed esophageal varices, necessitating multiple visits for esophagogastroduodenoscopy. Additionally, two of these patients experienced multiple episodes of cholangitis requiring hospital admission and antibiotic treatment. Three out of 5 patients still survived with their native livers.

KPE and pre-KPE referral pattern

Of 287 records of KPE, 91 were performed in HR-13 (31.7%), followed by 31 in HR-0 (10.8%), 29 in HR-12 (10.1%), 29 in HR-7 (10.1%), and 20 in HR-2 (7.0%) (Fig 3). Of 287 cases, the surgery was performed on their first admission in 234 cases (81.5%) when 51 (17.7%) had one admission before the definitive surgery and 2 (0.7%) had two prior admissions. In 53 referral cases, the average duration from the first hospital to the hospital where the patients underwent a definitive surgery was 9.2 days (range 1 day - 54 days). Most referrals occurred within the same health region (38 in 53 cases). Among 53 cases, 15 were trans-region referrals, of which 3 were referrals between non-adjacent regions. HR-13 (Bangkok) was the majority of referral destinations (11 in 15 trans-region referrals).

Referred cases had significantly poorer survival outcomes than cases that were operated on in the first hospital they were admitted to. When the two-year overall survival of those who were operated on at the first hospital was 78.26% (95% confidence interval (CI) 72.17% - 83.18%), the figure was 57.13% (95% CI 41.97% - 69.69%) (Log-rank p-value 0.002) in referred cases. (Fig 4)

DISCUSSION

As the first extensive national study to utilize data from the NHSO repository, this study included nearly all patients hospitalized with BA in Thailand, making it an ideal resource for analyzing the spatiotemporal distribution of diseases in the country. The crude incidence of BA in Thailand over the 6-year period was 1 in 5,500 live births, which is similar to that in other parts of Asia and aligns with previously estimated incidences in Thailand that

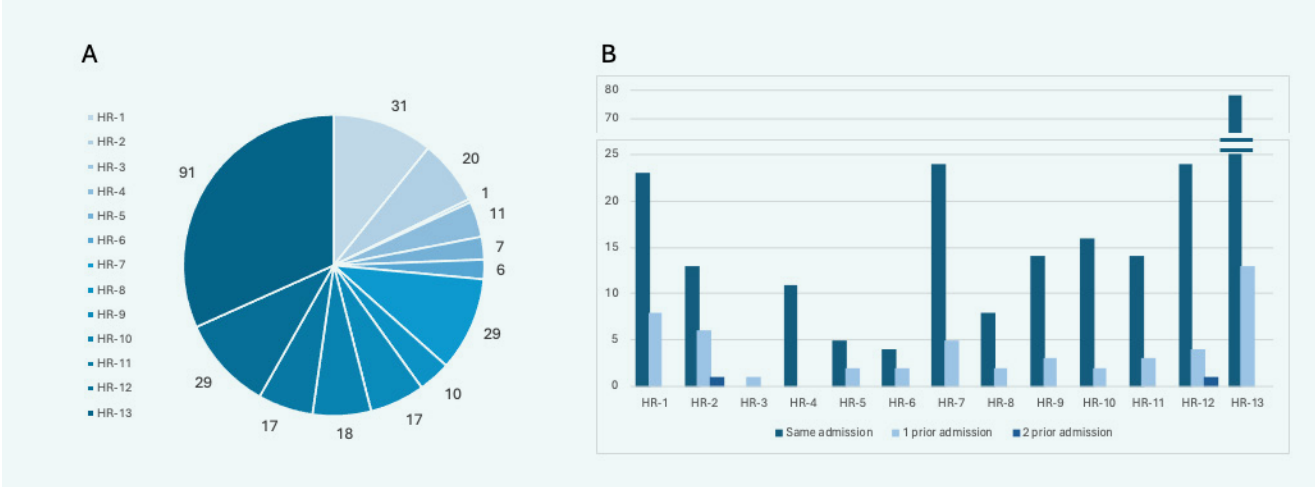

Fig 3. (A) Distribution in the number of Kasai's hepatoportoenterostomy (KPE) operations performed in each health region in Thailand during the study period. (B) Comparing the number of admissions before KPE in each health region.

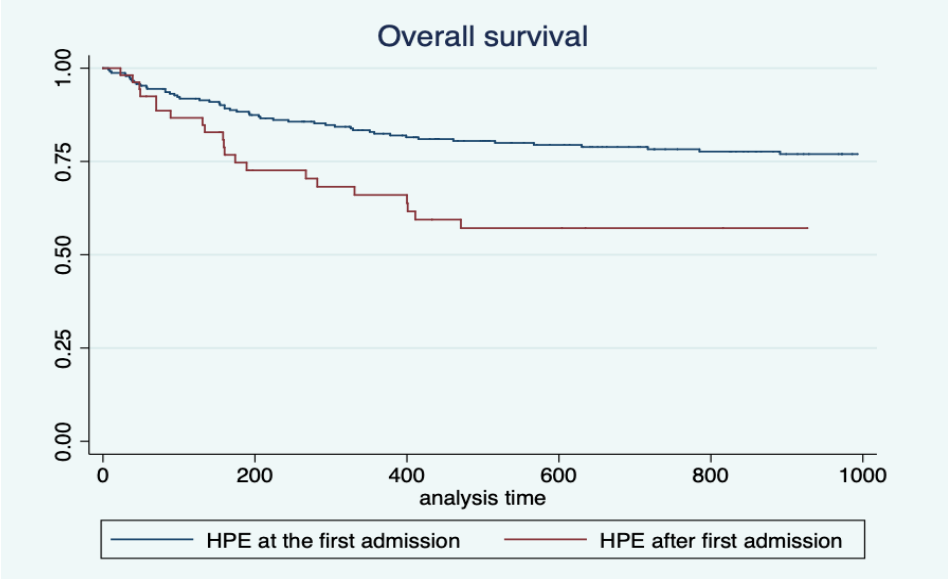

Fig 4. Comparing overall survival between those who underwent a Kasai's hepatoportoenterostomy (KPE) at the first admission and those who were operated on after their first admission.

ranged from 1 in 5,000 to 1 in 15,000 live births[13], but higher than those in Europe, Canada, and the USA.[2,4] The mean age of the patients at presentation was two months, and most of the first admissions occurred in 2017 and 2018, before the COVID-19 pandemic, followed by 2021 in the pandemic era. The COVID-19 pandemic seems to affect BA incidence, possibly due to the decreased accessibility to healthcare services during this period.

In general, diagnosis of BA is confirmed through direct observation of the porta hepatis in cases where an atretic gallbladder is present or via IOC when the findings are not apparent.[14] In our data, IOC was performed in only 19.6% of the cases, which is a notably low number and may be explained by the missing of IOC coding when it was performed as a part of the KPE operation. However, other hospital-based studies in Thailand have reported higher rates of IOC utilization; Chieochalakom et al. observed that all 81% of cholestatic jaundice patients in their study underwent IOC following hepatic scintigraphy or ultrasonography (US) before KPE[14], and Laohapensang et al. reported that 25 of 48 patients in their series (51%) underwent diagnostic IOC. Most omitting cases in their study included 11 patients presenting with atretic gallbladder.[15] Furthermore, Wirifai et al. found that in a tertiary care setting in the North Eastern part of the country, 25 of 26 patients underwent US, 17 of 26 underwent scintigraphy scans, and all patients eventually underwent IOC.[16] Taken together, it seems that the investigation might have been under-recorded rather than under-performed. However, our study advocates a guideline on the preoperative investigation to achieve an accurate diagnosis before a definitive operation.

Our study estimated that KPE was performed in 44% of BA patients in Thailand. The relatively low number of KPE in our data mining could be due to miscoding or overestimating the number of new cases. Another possible explanation was a significant delay in patient presentation, which can negatively affect survival outcomes and increase postoperative morbidity and mortality rates. Consequently, some surgeons discuss the prognosis of the surgery with the parents and opt not to do the surgery. Despite Thai pediatric cholestatic jaundice treatment guidelines recommending KPE before 60 days of age, the mean age at KPE in Thailand was relatively high (82-97 days), given the jaundice onset at around four weeks.[7,14,15,17] In contrast, studies from France, Japan, and Taiwan have reported a median age of 55-59 days for KPE.[1,18,19] We also found that most KPEs were conducted in major tertiary centers in Bangkok, Chiangmai, Khon Kaen, and Songkhla. Additionally, 70.8% of KPEs were performed on the first admission, and those who underwent KPE on subsequent admissions had significantly lower survival rates. This finding aligns with those of previous studies, indicating that the timing of KPE influences survival rates and jaundice clearance.[20,21]

LT was performed in 11.4% of BA patients, which is relatively low considering the success rate of KPE at around 50-60%. Studies from large centers in BKK have shown variable LT volumes, from 4-6 operations per year in each institute.[13,22,23] From 2016 to 2018, 4 pediatric liver transplantation programs in Thailand performed 97 LT operations, and 74% of the patients were diagnosed with BA.[24] In comparison, a USA study reported 441 LDLTs and 611 split deceased-donor LTs

over 12 years[25], and the Japan Liver Transplantation Society (JLTS) reported 2,057 LT operations for BA over 25 years.[26] Due to organ shortages, LDLT is the primary choice of hepatic transplantation in Thailand[13], with 70% of LT performed in BKK and 76.1% of these performed as primary transplants without prior KPE. Considering the referral system, major hospitals in BKK, along with four pediatric LT centers, play a major role in both the KPE and the LT. Large tertiary care centers in the northern, northeastern, and southern regions also contributed substantially to KPE operations. As our study found that referral might cause delays in the treatment and poor operative outcomes, establishing a service care plan for infants with cholestatic jaundice in each HR to shorten the referral path to KPE might improve the overall outcome.

On data mining by the Apriori algorithm, our study identified frequent comorbidities and complications in patients with BA, including anemia and liver-related issues, such as cirrhosis, coagulation defects, and portal hypertension, which affected 10-15% of patients. This suggests late presentation and subsequent delay in the definitive treatment of BA in Thailand. Cholangitis, a major complication of BA, typically occurs within the first year of KPE.[21,27,28] In our study, 6.7% of the admissions of BA in Thailand involved cholangitis, with an average of three episodes per patient. Among these episodes, nearly 10% occurred at the same admission with KPE and 7% on the subsequent admission, with number of episodes ranging from 1 to 9. The co-occurrence of progressive liver diseases (cirrhosis, hepatic failure, or portal hypertension), anemia, coagulation disorders, and malnutrition and liver transplantation status significantly affected survival outcomes. Cirrhosis occurred in 15.6% of patients, with 25% developing cirrhosis at the same admission of KPE and 92% before LT. Similar findings have been reported previously, with portal hypertension and cholangitis affecting a significant proportion of patients during long-term follow-up.[29-31]

The 2- and 5-year estimated survival rates in this study were 75.1% and 72.5%, respectively, which were consistent with previous reports. A large European study reported 5-year native liver survival rates of 41-55% and 10-year survival rates of 35–47% after KPE.[21] Japanese data indicated 5-, 10-, and 20-year survival rates of 63%, 54%, and 44%, respectively, with half of the patients developing cirrhosis by the age of 20 years.[32] A previous Thai study found that 66.3% of patients were alive with jaundice-free status with their native livers over a mean follow-up of 50.5 months.[33]

In summary, our study used data mining to study BA in a large reimbursement dataset in Thailand. The incidence rates of BA in Thailand were comparable to those in other Asian countries, and patients with BA in Thailand exhibit notably lower survival rates. The co-occurrence of progressive liver disease (cirrhosis, hepatic failure, or portal hypertension), anemia, coagulation disorders, and malnutrition, significantly contribute to poor survival outcomes. LT was an excellent rescue option but with limitation in the availability of service. A regional referral system as a service care plan and the availability of a transplantation program are recommended.

Data Availability Statement

The data used in this study was obtained from the Thai Health Information Portal (THIP) database, which registers national health records for individuals admitted to public hospitals in Thailand. Access to this data was approved through THIP's official data access procedures. Due to restrictions on patient privacy, the data is not publicly available but can be requested from the THIP with appropriate permissions.

ACKNOWLEDGEMENTS

We extend our gratitude to the statisticians for their assistance throughout the data analysis. We also wish to express our special thanks to Mr. Kyaw Ko Ko Htet of the Department of Epidemiology for his valuable contributions to the geographical analysis.

DECLARATION

Grants and Funding Information

No funding was received for this study.

Conflict of Interest

No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

Registration Number of Clinical Trial

Not applicable.

Author Contributions

K.S. ; Main author, data management, data analysis, and discussion. S.S. ; Co-author, data analysis. V.C. ; Co-author, data management. All the authors contributed to the conception and design of the study and approved the final version for publication.

Use of Artificial Intelligence

No artificial intelligence was used in this study.

Abbreviations

BA – Biliary atresia, KPE – Kasai hepatic portoenterostomy, THIP – Thai Health Information Portal, NHSO – National Health Security Office, UHC – Universal Health Coverage, LT – Liver transplantation, SD – Super-district, HR – Health region, BKK – Bangkok, ICD-10 - 10th revision of the International Classification of Diseases, CMV – Cytomegalovirus, US – Ultrasonography, IOC – Intraoperative cholangiogram

Ethics Approval and Consent to Participate

This study was approved by the Songklanagarind Ethical Committee (Reference No. REC.66-529-10-1) and conducted in compliance with the Helsinki Declaration. The data used was obtained from the Thai Health Information Portal (THIP), which is a national database that records hospital admissions. Since the data was de-identified and extracted from a government health data warehouse, individual patient consent was not required.

Human Ethics and Consent to Participate Declarations

Not applicable.

Consent for Publication

Not applicable. This study used anonymized, de-identified data from the Thai Health Information Portal (THIP) database. No individual-level patient data, images, or details requiring consent for publication are included.

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