

# An audit of infants presenting with cholestatic jaundice at a secondary hospital in Johannesburg, South Africa

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**Background.** Neonatal cholestatic jaundice is a common paediatric condition with a paucity of recent local data and a notable absence of locally influenced diagnostic algorithms.

**Objectives.** To describe the causes of cholestatic jaundice, investigations conducted and patient outcomes.

**Methods.** This was a retrospective file review of 96 patients presenting to the Specialist Clinic at Rahima Moosa Mother and Child Hospital in Johannesburg between 1 January 2014 and 31 December 2020. Clinical features, serum biochemistry at presentation, diagnostic investigations (haematological, radiological and histological), diagnosis and outcome were analysed during data collection.

**Results.** Ninety-six patients were included in the study. The median age of jaundice onset was at 2 months, while the median age of presentation was 3.3 months. Causes of jaundice fell into three main categories: 38 had biliary atresia (BA); 24 had another specific diagnosis; and 34 remained without an underlying diagnosis (idiopathic neonatal hepatitis). An overall mortality rate of 26% was noted at a median (interquartile range) age of 13 (5 - 24) months and it was highest in the BA group ( $n=14$ ; 56%).

**Conclusion.** The evaluation of neonatal jaundice requires a wide differential and expeditious referral to optimise outcomes and avoid complications. Many patients remained undiagnosed, and the overall prognosis was poor. The authors recommend the development of a locally relevant diagnostic protocol to minimise delays in the identification, diagnosis and treatment of neonatal jaundice.

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Neonatal jaundice can be visible in up to 47% of all newborns in low- to middle-income countries (LMIC).<sup>[1]</sup> While most instances resolve without incident, in the case of cholestatic jaundice, it may be one of the only signs of a severe underlying pathology.<sup>[2,3]</sup> Prompt recognition and referral of neonatal cholestatic jaundice has been linked to improved outcomes, irrespective of the final diagnosis.<sup>[4]</sup>

The European and North American Societies for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN/NASPGHAN) have updated their diagnostic algorithm, which streamlines the evaluation process for patients with cholestatic jaundice.<sup>[4]</sup> While it is able to inform our current practice, this guideline fails to account for local disease prevalence, differing neonatal screening programs, and availability of investigations. In contrast to high-income countries (HIC), South African (SA) data has demonstrated a predominance of idiopathic neonatal hepatitis (INH), as well as cholestatic jaundice secondary to infective causes<sup>[5]</sup> and as a result, blood and urine cultures, blood serology and viral assays form an integral part of our local diagnostic workup. However, it must be noted that these data are more than 30 years old; therefore, a more recent characterisation of this population group is needed.

High-income countries have seen a reduction in patients with INH with access to newer investigational techniques, such as next-generation gene sequencing<sup>[6]</sup> that has yet to become readily accessible in our setting. The role of genetic testing for neonatal cholestasis in an SA setting remains to be explored.

Biliary atresia (BA) is the most common cause of cholestasis in our setting, and outcomes remain poor.<sup>[5,7]</sup> Due to delayed referral and poor access to specialised healthcare, patients often present with advanced liver disease, which limits the opportunity

to perform a successful Kasai porto-enterostomy (KPE).<sup>[7]</sup> Any diagnostic protocol for cholestatic jaundice must therefore aim to identify children with possible BA early, and refer them urgently for specialised care.

To motivate for more efficient screening tools and referral pathways, and to inform a locally appropriate diagnostic algorithm, a better understanding of the current landscape of neonatal cholestatic jaundice is needed. Therefore, this study aims to describe the existing causes of cholestatic jaundice at a secondary hospital in Johannesburg, SA.

## Methods

A seven-year retrospective file review of patients assessed by the paediatric gastroenterology (GIT) department at Rahima Moosa Mother and Child Hospital (RMMCH) was conducted using patient files between 01 January 2014 and 31 December 2020. Patients presenting with the onset of cholestatic jaundice in the first three months of life were identified using the existing GIT Research Electronic Data Capture (REDCap) database of patients. The REDCap database holds patient hospital numbers, presumptive diagnosis and logs procedures such as liver biopsies. Cholestatic jaundice was defined as a conjugated bilirubin of more than 17  $\mu\text{mol/L}$  when the total serum bilirubin is 85  $\mu\text{mol/L}$  or less, or a conjugated fraction of more than 20% when the total bilirubin is more than 85  $\mu\text{mol/L}$ .<sup>[4]</sup> For the purpose of this study, INH was defined as neonatal cholestasis where no cause was found with routine investigations.

Data collected included baseline characteristics, presenting complaints, clinical features, biochemistry at presentation, diagnostic

investigations (haematological, radiological and histological), diagnosis and outcome at the time of data collection. Patients who were no longer active members of the GIT clinic were followed up until reaching an outcome of either resolution of jaundice, transfer back to the referral centre, liver transplant, demise, or loss to follow up.

No local standard protocols were available instructing the investigation and management of neonatal cholestatic jaundice; therefore, patients were managed at the discretion of the treating physician. Investigations were carried out in a stepwise approach and informed by the clinical and biochemical presentation; hence, not all patients underwent all investigations.

Patients who underwent metabolic testing were first tested for urine organic acids, plasma amino acids and urine reducing substances. Based on these initial tests further tests of pyruvate, lactate, very long-chain fatty acids, plasma bile acids, plasma carnitine profile and urine succinylacetone were tailored to the individual profile.

Prematurity increases the risk of cholestasis through delayed enteral nutrition, prolonged parenteral nutrition, hypoxia, infection, liver ischaemia, immaturity of bile acid metabolism, surgical procedures and multiple drug treatments.

Categorical variables were described using frequencies and percentages, whilst continuous variables were described using medians (with IQR) as the data were non-parametric. Correlations between variables were assessed using Fisher's exact test as the cell sizes were small (i.e. <5). A *p*-value of <0.05 was considered statistically significant. All data analysis was conducted in STATA 15.0 (StataCorp., USA). Ethics approval for this research was authorised by the Human Ethics Committee (Medical) of the University of the Witwatersrand (ref. no. M210244).

## Results

A total of 122 patients were identified for inclusion, of which 96 files (79%) were complete and available for analysis.

### Patient characteristics

Baseline patient characteristics are presented in Table 1. The referral facility was noted in 57 patient files (59%); 4 (7%) were referred by a private physician. The remainder (*n*=53) were referred from Gauteng (*n*=42/57 74%), Limpopo (*n*=5/57; 9%), Mpumalanga (*n*=5/57; 9%) and KwaZulu-Natal (*n*=1/57; 2%) hospitals. Nutritional status (weight-for-length measurements) was recorded in 83 patients, of which 65% was within normal limits. No patients were noted to be overweight.

### Causes

Causes of jaundice fell into three main categories: BA (*n*=38), idiopathic neonatal hepatitis (*n*=34) and other (*n*=24) (Table 1). The diagnosis of BA was made with an intraoperative cholangiogram when the patient was deemed to be a candidate for a KPE or confirmed histologically in those who already had clinical signs of cirrhosis and portal hypertension. In two BA patients, the diagnosis was based on strong clinical suspicion and laboratory findings, as both patients demised before a confirmatory biopsy could be performed safely. A quarter of patients received another specific diagnosis, including galactosaemia (*n*=6), hepatic sinusoidal obstruction syndrome (HSOS) (*n*=6), infections (*n*=5), prematurity (*n*=2), Alagille's Syndrome (ALGS) (*n*=2), biliary cyst (*n*=1), cystic fibrosis (CF) (*n*=1) and panhypopituitarism (*n*=1). Infections included septicaemia (*n*=2), congenital syphilis (*n*=1), and twins with hepatitis B infection. The latter two were admitted at another hospital, where both were diagnosed with a positive hepatitis B surface antigen (HBsAg) and high viral loads. Hepatitis B *e* antigen

(HBeAg) and antibody (anti-HBe) testing showed conflicting results in the twins, but their mother was HBeAg-positive and anti-HBe-negative. Investigations for other causes of cholestasis were negative. Both children were HBsAg-negative at follow-up. In 34 patients, no specific diagnosis was made.

### Presentation and investigations

Presenting signs and investigations for each group are shown in Table 1. Significant features associated with BA included the finding of pale stools (*p* < 0.0001), pruritis (*p* < 0.0001), hepatomegaly (*p* = 0.0073), and splenomegaly (*p* = 0.0015). There was minimal difference in hepatomegaly across the three groups; 77% of all patients had hepatomegaly. Patients in the INH group had a significant absence of pale stools (*p* = 0.0004). A  $\gamma$ -glutamyl transpeptidase (GGT) level >250 U/L and a GGT/ aspartate transaminase (AST) ratio >2 (*p* < 0.0001) were found to have a significant correlation with BA. None of the 45 serum  $\alpha$ -1 antitrypsin levels ( $\alpha$ 1AT) yielded a positive result. A total of 32 (33%) patients had galactose-1-phosphate uridylyltransferase (GALT) testing: 5 in the BA group; 15 patients in the INH group; and 12 patients in the remaining group. Six of the 32 GALT tests led to a final diagnosis of galactosaemia (19%). Additionally, 14 children (15%) received testing for other metabolic disorders (i.e. inborn errors of metabolism), however, none yielded a positive result.

Across all groups, 58 ultrasounds were recorded as being done, however, only 41 reports were available for analysis (71%). A total of 17 ultrasounds were reported as normal (41%), of which 71% belonged to the INH group. An absent or abnormal gallbladder was noted in 10 patients with BA, two patients with idiopathic jaundice and no patients in the other group. Forty-five of 47 (96%) liver biopsies done had results available for review. A total of 32 biopsies (71%) ultimately led to a final diagnosis. Only 19 biopsy results were available for patients in the non-BA groups (95%) and 6 of those led to a positive diagnosis (32%): 2 were diagnosed with ALGS and 4 with HSOS. In all other patients, the liver biopsy did not lead to a final diagnosis, including 11 patients in the idiopathic group. Of the remaining biopsies, two were inconclusive, and one specimen had suboptimal sampling.

### Outcomes

A total of 25 patients demised at a median (interquartile range (IQR)) age of 13 (5 - 24) months. The most significant proportion of these children belonged to the BA group, leading to mortality rates of 37% (*n*/N=14/38) in the BA group, 18% (*n*/N=6/34) in the idiopathic group and 21% (*n*/N=5/24) in the other diagnosis group; this included four patients with HSOS and one with cystic fibrosis. A KPE was performed in 14 patients (37%) with BA. Patients who had a KPE had a lower median age of presentation than those who did not have a KPE (4.7 months (IQR 2.9;6.3) versus 6 years (IQR 4.5;9.2) respectively). Of the eleven patients who were lost to follow up in the BA group, two had a KPE performed. Seven of these patients (50%) are alive with a native liver but 85% have developed portal hypertension. Five patients were successfully transplanted, and one was still awaiting a transplant. A total of 18 patients (19%) were ultimately discharged from the GIT clinic, most of whom were from the idiopathic group (*n*=15; 83%).

### Discussion

Early identification of neonates with cholestatic jaundice improves outcomes.<sup>[4,8]</sup> Despite this, patients in our cohort presented at a median age of 3.3 months, which was similar to findings in another local study where the median age at presentation for a KPE was 3.7

**Table 1. Baseline characteristics, clinical and investigation findings at presentation according to aetiology of patients presenting with neonatal cholestatic jaundice to the Gastrointestinal Specialist Team at Rahima Moosa Mother and Child Hospital**

	Biliary atresia	Idiopathic neonatal hepatitis	Other
Total, <i>n</i> (%)	38 (40)	34 (35)	24 (25)
Males, <i>n/N</i> (%)	14/38 (37)	24/34 (71)	12/24 (50)
Age at onset of jaundice (months), median (IQR)*	2 (0.4 - 3)	2 (1 - 3)	1.5 (0.3 - 2.3)
Age at presentation (month), median (IQR)†	5 (3.3 - 7.1)	2 (1.2 - 3.2)	3.1 (1.8 - 4.3)
Weight-for-length Z-score (%)			
Normal	2 (5)	7 (20)	4 (15)
Wasted (-3 <Z-score <-2)	6 (16)	2 (6)	0
Severely wasted (Z-score <-3)	27 (71)	18 (53)	17 (70)
Unknown	3 (8)	7 (20)	3 (13)
Pale stools, <i>n/N</i> (%)	18/30 (60)	2/33 (6)	4/24 (17)
Pruritis, <i>n/N</i> (%)	17/32 (53)	0/31 (0)	2/23 (9)
Cardiac lesion, <i>n/N</i> (%)	8/38 (21)	3/34 (9)	3/24 (13)
Dysmorphic features, <i>n/N</i> (%)	3/29 (10)	3/30 (7)	1/15 (7)
Hepatomegaly, <i>n/N</i> (%)	35/38 (92)	24/34 (71)	16/24 (67)
Splenomegaly,	27/38 (71)	13/34 (38)	9/24 (38)
Ascites,	6/38 (16)	1/34 (3)	4/24 (17)
Results, median (IQR)			
Total Bilirubin(umol/L)	212 (162 - 255)	284 (179.8 - 369.5)	175 (86.5 - 279.5)
ALP (U/L)	878 (604 - 1 082)	644,5 (492 - 1 163.5)	966 (661 - 1 095.8)
GGT (U/L)	601 (337.5 - 1 249.8)	125 (72.5 - 202)	181 (79 - 343)
ALT (U/L)	126 (89 - 204)	139 (67.5 - 225.5)	71.5 (53 - 233.3)
AST (U/L)	242.5 (152.8 - 315.8)	294 (136.5 - 564)	221 (126.3 - 448.5)
GGT/AST ratio	2.7 (1.4 - 4.8)	0,4 (0.2 - 1)	0.7 (0.3 - 1.5)
Albumin (g/L)	31 (25 - 35)	30 (26 - 36)	30 (22.5 - 39)
Haemoglobin (g/dL)	10.8 (9 - 11.4)	11,5 (9.1 - 13.7)	9.7 (8.9 - 10.8)
Platelets (×10 <sup>9</sup> /L)	248 (186 - 389.5)	201(94 - 355.5)	215 (84 - 323.3)
Ultrasound reports			
Ultrasound report documented, <i>n/N</i> (%)	17/38 (45)	15/34 (44)	9/24 (38)
Gallbladder small or not seen, <i>n/N</i> (%)	10/17 (59)	2/15 (13)	0
Gallbladder collapsed, <i>n/N</i> (%)	2/17 (12)	1/15 (6)	2/9 (22)
Normal ultrasound, <i>n/N</i> (%)	1/17 (6)	12/20 (60)	4/9 (22)
No available comment on gallbladder, <i>n/N</i> (%)	4/17 (24)	1/20 (5)	3/9 (33)
Liver biopsy documented, <i>n/N</i> (%)	28/38 (74)	11/26 (42)	8/20 (40)
Bile duct proliferation, <i>n/N</i> (%)	23/28 (82)	2/11 (18)	1/8 (13)
Paucity of bile ducts, <i>n/N</i> (%)	0	3/11 (27)	3/8 (38)
Cirrhosis, <i>n/N</i> (%)	12/28 (44)	0	2/8 (25)

IQR = interquartile range; ALP = alkaline phosphatase; GGT = gamma-glutamyl transpeptidase; ALT = alanine transaminase; AST = aspartate transaminase.

\*Age at onset of jaundice onset was known for 64 patients (67%).

†Age of presentation was known for 95 patients (99%).

months.<sup>[7]</sup> By comparison, in a high-income setting only 12% of their population presented after three months of age.<sup>[9]</sup> In SA, barriers to accessing healthcare, decentralisation, poor health-seeking behaviour, and lack of readily applicable neonatal screening programmes have all contributed to delayed diagnosis and presentation.<sup>[4,7,10]</sup> Delayed diagnosis is compounded by poor recognition of jaundice even among healthcare workers. Several studies demonstrate that jaundice is only visually apparent when total serum bilirubin exceeds 42 - 51 mmol/L and only 63% of healthcare workers are able to identify the presence of acholic stools.<sup>[4]</sup> Additionally, SA's integrated management of childhood illnesses (IMCI) guidelines do not prompt healthcare workers to perform a total and conjugated bilirubin, or contain visual aids like stool colour charts, potentially delaying diagnosis even further. Delay in presentation risks irreversible disease progression

and limits available choices in treatment modalities. This is supported by the high rates of splenomegaly at initial presentation among patients with BA (71%), indicating the presence of biliary cirrhosis and portal hypertension. Delayed presentation limits the opportunity to perform a timely KPE to achieve bile drainage and impacts long-term survival of infants with their native liver.<sup>[4,5,7,11]</sup> Presently, local paediatric surgery centres perform KPE at a median of 91 days<sup>[7]</sup> compared with North American centres where the median age is 63 days.<sup>[12]</sup>

BA and INH account for up to two-thirds of all cases of neonatal cholestatic jaundice in high-income settings;<sup>[13]</sup> however, limited data are available from developing countries. These two entities made up 78% of our cohort, primarily owing to increased numbers of idiopathic neonatal jaundice compared with other centres, especially in high-income settings.<sup>[2,9,14,15]</sup> Concerningly,

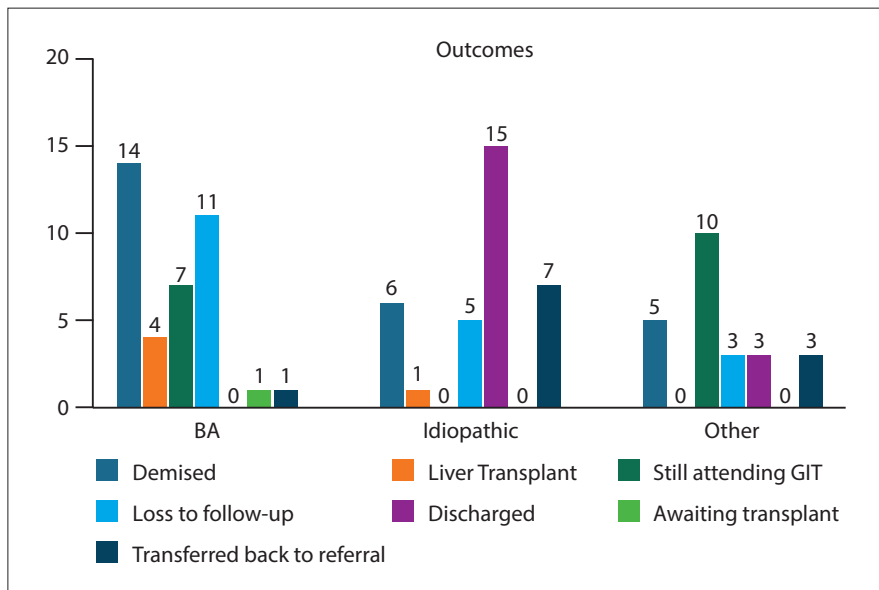


Fig. 1. Outcomes of patients with neonatal cholestatic jaundice in each diagnostic sub-category (n=96)

the proportion of patients with INH (35%) in the present study was similar to the proportion found by Motala *et al.*<sup>[5]</sup> in 1990 (36%), illustrating that very little progress has been made in characterising this patient group. With the reduction of cost and increased accessibility to targeted gene panels and next-generation gene sequencing (NGS), many INH patients can now be diagnosed with specific monogenic causes of cholestasis.<sup>[4]</sup> The diagnostic yield of NGS in this population is variable, with one study showing a 12% yield<sup>[16]</sup> and up to 60% in another.<sup>[6]</sup> This would suggest that it may not be a diagnostic silver bullet but instead relies on a combination of focused clinical suspicion and judicious use of resources. A higher yield has been shown after excluding possible causes of transient neonatal cholestasis such as sepsis, asphyxia, prematurity, surgery, invasive ventilation, and haemodynamic instability,<sup>[8]</sup> in addition to testing children with the highest likelihood of a genetic aetiology.<sup>[17]</sup> Achieving a diagnosis in this group has allowed for better counselling of parents and families, the ability to prognosticate conditions and improved our ability to use phenotypes to anticipate outcomes.<sup>[17]</sup>

We found an incidence of 6% of hepatic sinusoidal obstruction syndrome (HSOS), a condition not frequently encountered in high-income countries. HSOS is a known consequence of pyrrolizidine alkaloid ingestion, a substance occasionally found in traditional SA remedies.<sup>[18]</sup> Unfortunately, outside of oncology, there are limited data available documenting the incidence and natural progression of this condition. Nevertheless, we know that it is associated

with a considerable mortality rate, especially in children under 5 years of age.<sup>[19]</sup> Our cohort showed a mortality of 67%.

Presently there is no national screening programme for galactosaemia in SA, despite it being the most common inborn error of carbohydrate metabolism in SA.<sup>[20]</sup> Galactosaemia comprised 6% of all infants presenting with cholestatic jaundice and 25% of all infants in the 'other' category, further highlighting its relative frequency.

Motala *et al.*<sup>[5]</sup> found a higher prevalence of infectious causes of cholestasis which was not reflected in our study (24% v. 5%). While SA has seen improvements in antenatal screening programmes, we fear that this may be a result of our study setting where not all patients with what was perceived as 'transient' neonatal cholestatic jaundice were referred to the GIT team.

As treating physicians tailor investigations in the absence of local consensus guidelines, we see a varied approach with each patient. Owing to the lack of national neonatal screening programmes, delayed patient presentation and laboratory waiting times, initial assessment necessitates a broad diagnostic approach to expedite the initiation of interventions. In keeping with existing data, we found a significant correlation between BA and increased levels of GGT and GGT/AST ratio.<sup>[11]</sup> We also found a high diagnostic yield of liver biopsies (71%), reiterating its importance in the diagnostic workup of infants with cholestatic jaundice.<sup>[4]</sup> Unlike existing studies, we did not find a significant association between high levels of AST and INH.<sup>[11]</sup>

In our setting, while ultrasounds are an easily available and non-invasive

imaging modality to assess for biliary tree obstructions or cysts, operator-dependent variability and fasting status of the patient decrease its sensitivity.<sup>[4,11]</sup> Unfortunately, due to the lack of an available picture archiving and communications system (PACS) for storing and retrieving ultrasound reports, only 43% of patients were noted to have a documented ultrasound; however, we suspect the number may be much higher. Interestingly, in addition to patients with BA, an absent or abnormal gallbladder was noted in two patients with idiopathic jaundice (13%), while at least one patient with BA was documented to have a normal liver ultrasound. This confirms that the presence or absence of abnormal gallbladder alone cannot confirm or exclude the diagnosis of biliary atresia. Instead, the use of pale stools and high GGT is a better indicator to guide practitioners to motivate for confirmatory investigations such as an intraoperative cholangiogram. Although the use of ultrasounds are a useful modality for the inclusion or exclusion of other pathologies (e.g. choledochal cysts).

ESPGHAN/NASPGHAN guidelines advise the exclusion of  $\alpha$ 1AT, ALGS and CF early in their algorithm as the clinical picture and the histological findings of  $\alpha$ 1AT, ALGS and CF can mimic that of BA.<sup>[4]</sup> Caucasian population groups see a higher relative frequency of  $\alpha$ 1AT than African populations (7.7% v. 4%, respectively).<sup>[5,13,21]</sup> There were no positive findings in the 45 patients (47%) we tested for an  $\alpha$ 1AT deficiency. *SERPINA1* gene, (which encodes  $\alpha$ 1AT) mutation testing is not routinely done locally unless there is a high index of suspicion an  $\alpha$ 1AT deficiency.

We found an overall mortality rate of 27% (across all groups), with the probability that this number may be greater given our 22% rate of loss to follow-up. In our BA group alone, we found the mortality to be at least 37%, which was higher than rates seen in HIC.<sup>[8]</sup> We attribute our low numbers of KPE to the delay in presentation associated with advanced liver disease; as a result, KPE is unlikely to improve outcomes. Alongside earlier diagnosis and referral, centralisation of surgical care may also lead to better patient outcomes.<sup>[4,7,10]</sup>

The idiopathic group likely contains patients with transient cholestasis, as is reflected by the high proportion of patients discharged from the clinic ( $n/N=15/34$ , 44%). It also contains patients whose cholestasis is not transient: 6 demised; 1 was transplanted; and 1 is still in follow-up. The authors are eager to advocate for genetic testing for this group of patients. The



prevalence of many monogenic causes of cholestasis (e.g. progressive familial intrahepatic cholestasis, Niemann-Pick disease type C, etc.) in Southern Africa is unknown. Multicentre studies investigating this group of patients, possibly using whole-exome sequencing, is called for.

Lastly, in the 'other diagnosis' group, mortality was highly cause-dependent; two-thirds of infants with HSOS demised, compared with none of the infants with galactosaemia.

### Study limitations

As we conducted a single-centre study, generalisability was limited. The retrospective nature of the study results in the possibility of reporting bias. At least one-fifth (21%) of patients' files could not be retrieved, and the lack of a PACS for retrieving ultrasound reports has resulted in the likelihood that all ultrasounds could not be included and analysed in the present study. In addition, not all patients with transient causes of cholestasis were referred to the GIT specialist team and they may have been underrepresented. Additionally, referral bias may have led to an overrepresentation of patients with BA in this group.

### Conclusion

Neonates with cholestatic jaundice in SA represent a group of patients with insufficient recent local data and who could significantly benefit from better recognition, diagnostic and referral practices. To the best of our knowledge, this is the first paper within the last 30 years reviewing the incidence of causes of neonatal cholestatic jaundice in SA. Worryingly, we noted minimal change in the frequency of patients diagnosed with INH. We hope the present study serves as a basis for ongoing research, and the development of local screening algorithms.

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