LATE PRESENTATION BILIARY ATRESIA AT THE CHRIS HANI BARAWANATH HOSPITAL: A RETROSPECTIVE STUDY

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DECLARATION

I, Refiloe Relebohile Moreke, hereby declare that the work on which this dissertation is based on is my own original work (expect where acknowledgements indicate otherwise). It is being submitted for the degree of Master of Medicine in Paediatrics at the University of the Witwatersrand. This work has not been submitted or presented before for any degree or examination at this University or any other institution.

Signed :……

On this:…… day of:……..2019

DEDICATION

To my beloved husband Motheo and my precious children Letlotlo and Lethabo, thank you for the amazing support you have shown me throughout this journey. To my mother 'Marefiloe, my biggest supporter and lastly to my sisters Ithabeleng, Itumeleng and Mpho thank you for being my rocks.

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ABSTRACT

BACKGROUND: Biliary atresia (BA) is a destructive inflammatory obliterative cholangiopathy, which if untreated, can lead to liver cirrhosis and death by age of 2 years. Surgical intervention is the only therapy that improves prognosis if performed at < 90 days. In affluent countries, liver transplantation has improved outcomes in children with BA. In limited resource settings, Kasai hepatoportoenterostomy (KPE) remains the standard of care for children with biliary atresia.

OBJECTIVES: To identify and describe the subgroup of infants with BA who were 90 days or older at presentation and to identify factors contributing to the late presentation and document the management and outcomes of these children.

METHODS: All infants diagnosed with BA at Chris Hani Baragwanath Academic Hospital (CHBAH) between January 2010 and December 2015 were included in the study. Presenting signs and symptoms were compared between early and late presenters. Parental and medical factors contributing to late presentation were investigated. Management and outcomes of the late presenters were recorded.

RESULTS: BA was diagnosed in 122 infants during the study period. Of the 102 cases analysed, 49 (48%) were identified as late presenters, with a median age at presentation of 3) 172 days (IQR 119.5; 193.5). Both parental and medical factors contributed to late presentation. Parental factors primarily related to inability to recognize persistence of jaundice as abnormal. Factors at all levels of health care included lack of awareness of significance of prolonged jaundice of greater than 14 days and misdiagnosis of the condition.

Of the 49 late presenters, 13 were offered laparotomy, with KPE performed on 10 of these patients. Clearance of jaundice at 6-month post KPE was only documented in 2 patients. Six of the 49 patients were referred for liver transplantation. Of these 1 was transplanted, and 4 were listed, of which 3 demised while on the waiting list and 1 was waiting to be listed. As of January 2017, 10 patients were still alive, 12 known to have demised and the rest were lost to follow up.

CONCLUSION: Nearly half of our patients presented late. Both parental and medical factors contribute to the late presentation of patients with BA. We advocate for educating the community and medical personnel of the detrimental effect of late presentation of BA. Increased awareness is essential, as only a handful of late presenters can be offered KPE and or liver transplantation.

LATE PRESENTATION BILIARY ATRESIA AT THE CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL: A RETROSPECTIVE STUDY

Biliary Atresia (BA) is a destructive inflammatory obliterative cholangiopathy of neonates that affects varying lengths of both intrahepatic and extra hepatic bile ducts. If untreated, progressive liver cirrhosis leads to death by age 2 years. [1]The reported incidence of BA varies from 1/17 000-1/19 000 live births in the United kingdom (UK) and France, to 1/5 000 live births in Taiwan. The incidence of BA in the black population in Soweto, Johannesburg South Africa, was found to be between 1 in 2500 to 8000 live births. [2] It is essential to differentiate between physiological and pathological jaundice in the new-born with jaundice persisting beyond 14 days of life. Typically, BA presents shortly after birth with persistent jaundice, dark urine and pale stools. [3] Infants are usually full term and manifest with normal growth and weight gain during the first few weeks of life. Hepatomegaly may present early, and the liver is often firm or hard to palpation. Splenomegaly is common. Direct hyperbilirubinaemia (greater than 2mg/dL or less than 20% of total bilirubin) is always an abnormal finding. Investigations should be directed to identifying BA in these patients and to refer them early for surgical intervention.

No primary medical treatment is available for the management of BA. Surgical intervention is the only mechanism available for definitive diagnosis (intra-operative cholangiogram) and therapy. Kasai hepatoportoenterostomy (KPE) and liver transplantation remain the cornerstone of treatment in children with BA. Half of all paediatric liver transplants performed worldwide are for BA.[4] KPE can achieve complete clearance of jaundice, restore excretory and synthetic liver function, and enable healthy growth and development. However, this outcome is neither certain nor predictable from the outset. In view of the heterogeneity of the condition and other contributing factors, early identification of the condition will be only one of many ways of improving outcomes in children with BA. Other factors affecting prognosis include coexistent congenital malformations, liver histology at surgery, peri-operative medical management and centralization of care.[3] The success of KPE is measured by the clearance of jaundice; and is defined as achievement of normal bilirubin concentrations within 6 months of the procedure [5]. Early resolution of jaundice has been reported as 60-80% in the UK [5] as compared to recent local reported rate of 28 %. [6] Many factors are known to affect success of this surgery. These include age at surgery, extent of liver damage and surgical expertise. [5] Numerous studies have shown better surgical outcome in patients younger than 60 days old at the time of surgery, however the optimal timing of the surgery remains controversial.[5,7,8] The prognosis for patients aged >3 months at the time of surgery is generally poor [14]. KPE is a palliative procedure and does not cure BA [3]. The disease progresses in 70% of children in whom bile drainage is established, with development of fibrosis, portal hypertension and cirrhosis [3]. Despite this fact, more than 80% of those who have had a successful procedure survive longer than 10 years with their native liver with good quality of life [3]. Indications for liver transplant depend on the success of the KPE and the rate of development of complications. In our resource poor setting, liver transplantation is inaccessible to the majority of our patients with chronic liver disease.

The aim of the study was to primarily analyse the subgroup of infants who were 90 days or older at the time of presentation with BA. The 90 days cut off was informed by studies that alluded to the fact that the prognosis of KPE for BA worsens when the age at surgery increases and looked at a cut off of 90 days for surgery [9]. To also identify factors contributing to late presentation and document the outcome in these children. A local MMed thesis (to our best knowledge as yet unpublished) from Red Cross War Memorial Children's Hospital, in reviewing the age of presentation, clinical course and outcome of all infants presenting to RCWMCH with biliary atresia, did record amongst their findings, poor parental knowledge resulting in delayed health seeking behaviours, distance from health care facilities and financial constraints limiting access to medical services, high work-loads and lack of awareness regarding causes of prolonged neonatal jaundice amongst primary health care staff resulting in inappropriate advice being given to parents and delayed referral as causes of late presentation in children with BA in South Africa [10]. Differences (or similarities) in the management and outcomes were not compared between early and late presenters in this study, because those results are available and published in a study performed by the Chris Hani Baragwanath Academic Hospital CHBAH Paediatric Gastroenterology, Hepatology and Nutrition Unit (PGHNU) (6). Propose suggestions of addressing factors contributing to late presentation in the South African population, ultimately aiming to increase awareness of the condition amongst the community and medical personnel. In the process, encourage the development of a screening protocol for BA to encourage early presentation and referral.

Objectives

The main objective was to determine the prevalence of patients with late presentation BA (>90 days of age) seen at the Chris Hani Baragwanath Academic Hospital CHBAH Paediatric Gastroenterology, Hepatology and Nutrition Unit (PGHNU) between January 2010 and December 2015 and attempt to identify factors that might have contributed to the late referral or presentation. Secondary objectives included comparison of the clinical characteristics between early (≤90 days of age) and late presenters at first presentation, and documentation of management and outcome of the late presenters. Comparison of outcomes of early and late presenters has been previously documented and published from the same Unit [6].

Methods

Setting and participants

A retrospective analysis was done at a single tertiary academic hospital in Johannesburg, South Africa. Inclusion criteria were all children with BA presenting at CHBAH between January 2010 and December 2015. Late presenters with BA were followed, up to the 31st of January 2017.

Data collection

Data were obtained from the CHBAH PGHNU clinical records and database and entered onto a prepared data collection sheet. The data sheet captured demographic data, information on patient contact with health care professionals, history of referral, presenting history and clinical features, on all patients diagnosed with BA during the study period. Growth parameters were assessed using World Health Organisation (WHO) z-score values for weight and height for age. Weight and height values were converted to z scores using WHO AnthroPlus software. [12] Patients were assessed based on height for age (HFA) z scores as: normal (> -2), stunted (between -2 to -3) or severely stunted (<-3). Patients were also assessed based on their weight for height (WFH) as: normal (>-2), wasted (between -2 to -3), severely wasted (<-3). Malnutrition was assessed based on weight for age (WFA) as: moderate (between <-2 and -3) and severe (< -3). Management and outcome were only documented on late presenters.

Early presentation was defined as presentation at ≤ 90 days of life, while late presentation was presentation at > 90 days of life. Management was divided into medical alone or combined medical and surgical management. Surgical management was subdivided into laparotomy only or laparotomy with KPE. The small number of late presenters who underwent KPE were documented as having a functioning (anicteric with pigmented stool), partially functioning (icteric with pigmented stool), or non-functioning (icteric with acholic stool) KPE, at 3 months and 6 months post-surgery. Outcomes recorded included whether patients were still alive at the end of the study, follow up period with their native liver and the number referred for liver transplantation. The cut off for follow up for the late presenters was set as 31st January 2017. Patients who were lost to follow up were censored at the time of their last visit.

Statistical Methods

Data collected was entered onto a Microsoft excel spread sheet and basic statistical analysis performed using Microsoft Excel. Appropriate descriptive statistical analysis using percentages and means or medians were used. Continuous data has been presented as medians with first and third interquartile (Q1 to Q3) and categorical data presented as percentages. All statistical assessments were considered significant for a p-value below 0.05.

For more detailed statistical analyses, a statistical program SPSS was utilised. In case of unavailable data, participants were excluded from being part of the analysis.

Ethics permission was obtained from the University of the Witwatersrand (Wits)'s Human Research Ethics Committee (Medical) (ref.no.M160967)

Results

There were 122 patient records retrieved with BA, diagnosed during the study period, 1st January 2010 to 31st December 2015, of which 20 were excluded from the study due to incomplete data.

Demographics including age, sex, province of residence and maternal education are shown in Tables 1, 2 and 3.

Clinical signs and symptoms: early vs. late presenters

The presenting history and clinical signs of the 102 patients with BA are shown in Table 1. History of stool colour was documented in 89 patients, but only confirmed on examination, by admitting doctors, in 62 of the 102 patients. Of note, there was a significant number of patients whose stool and urine colour were not examined despite the presence of jaundice. The only significant difference in growth parameters between the two groups was evidence of stunting in the late presenters. Significantly, a greater number of mothers reported acholic stools in the early presenters as compared to the late presenters, which may explain the earlier presentation. Splenomegaly, digital clubbing and rickets (craniotabes, rachetic rosary, wrist widening) were significantly more prevalent in the late presenters with chronic cholestatic liver disease. No BA associated congenital malformations such as situs inversus, intestinal malrotation or polysplenia/asplenia were diagnosed in the late presentation population of children with BA. However one of these patients was confirmed to have the cystic BA variant at laparotomy. The study did not look into whether any of the early presenters presented with BA associated malformations.

Factors contributing to late presentation BA:

Reasons for late presentation were available in 47 of the 49 patients. In the majority of late presenters, a combination of factors contributed to the late presentation. Documented reasons for late presentation included:

1) Parental factors: 20 mothers thought the jaundice was normal, 6 failed to ever present to a primary health care facility and 4 defaulted follow up appointments at clinics/hospitals.
2) Medical factors:
   Primary health care facilities: 15 patients were given false reassurance (jaundice assumed to be due to physiological jaundice or breastfeeding jaundice) and 3 although not referred then, were given follow up appointments for review.
   District hospitals: Four patients were seen at district hospitals and not referred to a tertiary centre. One was misdiagnosed as sepsis, treated and discharged, 1 was falsely reassured and not investigated, 1 was investigated but no action was taken on abnormal laboratory results and 1 patient was given a follow up appointment for review.
   Tertiary centre: One patient was diagnosed with an Escherichia Coli urinary tract infection, and the underlying BA was missed and confirmed at a later presentation.

Preference for traditional medication use or reluctance for surgical intervention were not given as factors in any of the patients. Histological misdiagnosis was also not documented as a cause for late surgical referral.

Management of late presenters

All 49 late presenters underwent a liver biopsy to confirm diagnosis and assess degree of liver fibrosis at presentation. Nineteen patients were referred for surgical management (Table 2). Although 13 patients were referred for KPE, macroscopically cirrhotic livers noted at time of laparotomy precluded performance of the procedure in 3 patients. KPE was performed on 10 patients, and the median age at KPE in these patients was 112 days (IQR 105.25; 120.75). Early resolution of jaundice defined as achieving bilirubin levels less than 34µmol/L by 6 months post-surgery was achieved in 2 of the 10 patients. Of the remaining eight, 4 were partially functioning (icteric with pigmented stool), 3 were non-functioning (icteric with acholic stool) and 1 demised post-operatively. The remaining patients were managed medically with nutritional modification, and vitamin and mineral supplementation. As their disease progressed complications of portal hypertension and pruritus were managed on an individual basis.

Outcome of late presenters

The median follow up for the late presenters was 11 months (0; 53). By 6 months post first presentation, 28 (57.1%) patients were still alive, 14 (28.6%) were already lost to follow up and 7 (14.3%) were known to have demised. By 12 months: 19 (38.7%) patients were still alive, 20 (40.8%) were lost to follow up, 9 (18.4%) were known to have demised and 1(2.1%) was referred to private health care. As of 31st January 2017, 10 (20.4%) patients were still alive and 12 (24.5%) confirmed to have demised. Documented causes of death included: 1 due to post-operative complications related to KPE procedure, 1 due to advanced retroviral disease, 1 due to an upper gastrointestinal tract bleed, and in 9 patients, causes were unknown. Overall follow up attendance was poor. Nine patients never made it to any follow up appointments post discharge and were presumed to have demised and 16 patients were initially followed up, but discontinued clinic attendance at varying time intervals and were also presumed to have demised. Based on documented Wits Donald Gordon Medical Centre transplant data, none of the defaulters were transplanted up to the 31st of January 2017.

Discussion

Nearly half of all patients who presented with BA during the study period were late presenters. Factors for late presentation or referral were identified across all levels of health care. Contributing parental factors were also identified.

The survival rates in children with BA in South Africa are poor as compared to more affluent countries. In developed countries, 5 year native-liver survival rates of up to 60% and overall 5-year survival rates of up to 90 % have been reported [13], whereas a local study has shown a 2-year native liver survival rate of 19 %. [6] The majority of patients are from poor socio-economic backgrounds with difficulties in accessing health care services and often relying on primary health care services to refer them to a tertiary level hospital should the need arise. Late presentation BA is a recognised problem in South Africa. Children with BA present late, with more than a third not able to receive KPE due to late presentation and established cirrhosis.[6] Our study confirms the high prevalence of late presentation and documents the poor outcome in these children.

The etiological heterogeneity of BA is complex. Timeous diagnosis and referral will be one of many factors that would need to be addressed to ultimately improve outcomes in children with BA. Other factors which may affect the success in our population include lack of management protocols and limited resources in terms of accessibility to the best medical, nutritional and post-operative care. A lot of attention has been paid to the age at the time of the operation with a better surgical outcome expected in patients younger than 60 days old at the time of surgery.[14] However KPE has been known to be successfully performed in a limited percentage of children up to 100 days or older, suggesting that referring for surgery should be based on an individual basis and clinical picture. [5,15] This was reflected in our study as well. Although KPE outcomes performed at all ages in RSA are not as successful, when compared to more affluent and well-resourced countries, the procedure still allows infants with BA the opportunity to achieve bile drainage with their native liver, improve survival rate and delay the need for transplantation. The majority of our late presenters, without surgical intervention, demised within the first 2 years of life, in keeping with previous documented studies.

Malnutrition is a significant clinical problem in children with BA, particularly in the first year of life and has been shown to increase morbidity and mortality risk post KPE and liver transplantation. [16] Assessment of nutritional status in patients with chronic liver disease is difficult and imprecise. This is because indicators of nutrition on assessment are confounded by the presence of significant visceromegaly, oedema and ascites. Body weight alone can result in erroneous representation of nutrition in these patients. This might explain why the only growth parameter that was statistically significant between the early and late presenters, was height for age (stunting). Mid upper arm circumference (MUAC) is a more reliable representation of nutritional status as compared to weight for age (WFA), height for age (HFA) and weight for height (WFH) and should be used more often in children with chronic liver disease. [17]

Although yellow discoloration of the skin and conjunctiva was present in all patients, this did not necessarily translate into early presentation or investigation and referral. Examination of stool colour was also shown not to be routinely performed even at tertiary hospital level. The presence of pale stools is a sensitive marker for cholestatic liver disease, but parental reports of the history of pale stools can be misleading. [18] However of note in our study, more parents in the early presenter group complained of pale stools as compared to the late presenter group. This was unclear why from the study. However possible reasons could be that these parents had experience with previous children who had normal stool colour or that they were more observant and/or aware of what may be considered an acceptable stool colour. Stool colour should be assessed in all patients presenting with prolonged jaundice to assist in the diagnosis of BA. Stool colour charts (showing different normal and abnormal stool colours to be compared with baby's stool), have been used successfully in Taiwan since 2004 [7] .These could either be placed inside the road to health booklets or posters with the same stool colour charts could also be displayed in waiting rooms in the clinics or secondary level hospitals. The stool chart is a simple and effective measure. The UK introduced the 'yellow alert', an educational program aimed at expediting the referral of jaundiced patients to tertiary centres for investigation and treatment if required. [18] A similar approach can also be undertaken by ensuring that algorithm posters regarding management of a child with jaundice are available in local PHC to ensure early detection and referral of cholestatic children.

The rapid progression of BA to cirrhosis and portal hypertension was reflected in the differences in the clinical presentation between the two groups. We hope the documentation of various clinical presentations will increase awareness of the condition.

A number of local studies have documented that late presentation of BA is a problem in RSA [2,6] more so than in the rest of the world.[5] Our study went further and identified factors that contributed to the delay in presentation and noted these to include both parental and health care worker related reasons. Our results are comparable to overseas studies documenting causes of late presentation, such as, failure of the patient's parents to attend any form of health check regarding persisting jaundice, repeated reassurances by primary health care workers, significant delay in referral by the general practitioner and misdiagnosis in the referring hospital. [5, 19, 20,21] Our study attempted to correlate maternal education with delayed presentation, but due to limited data a conclusive association could not be made. However we believe emphasis should be placed on educating not only the community but also health care personnel, highlight the significance of persistent jaundice of greater than 2 weeks duration, and accentuate the necessity for inspecting and documenting stool colour in a jaundice child. These measures would promote early identification of the condition and expedite referral for better outcomes.

The majority of children with suspected established cirrhosis were excluded from surgical intervention as offering KPE to these children was unlikely to result in a successful outcome. Only a small percentage of late presenters had successful KPE, leaving a large number of patients which should have been ideally referred for liver transplantation. However, liver transplantation still remains a scarce resource in South Africa and is only available to a small percentage of our patients with BA. [22,23,24,25] Some of the reasons for non-referral include; psychosocial issues, poor socio-economic circumstances, inadequate family support systems, lack of accessible transport, scarcity of donor livers, delays in diagnosis and limited remuneration from the National Department of Health. The increasing accessibility to the public patients, of cadaveric or related living donor transplantation within the private sector, has expanded the donor pool and increased referrals and number of liver transplantations performed. Discussion is ongoing as to when to stop offering KPE in the older child with BA and rather refer directly for liver transplantation in resource rich settings, as evidence has shown that previous abdominal surgery increases risk of complications such as intestinal perforation post transplantation. [5]

Long term outcomes were only available in a small percentage of the late presenters as a large number defaulted follow up appointments. This may be explained in part by the poor prognosis of the condition, but other factors are thought to be contributing as well. Improving patient health literacy with education can empower patients to make better care decisions regarding their children's health; improve compliance with medication and follow up appointments, and even promote earlier identification of abnormal clinical signs and symptoms ensuring earlier presentation to medical facilities.

Limitations

The study is a retrospective study and therefore data was collected from an existing database. We relied on patients records for information regarding reasons for the late presentation and this was unfortunately not always asked. The department does not have a template for this information. In case of unavailable data, participants were excluded from part of the analysis. In view of a high attrition number in follow up appointments, confirmed outcomes for the late presenters were available in a minority of the patients with the majority assumed to have demised. Lack of details regarding direct causes of death in patients known to have demised, was also a limitation. Direct clinical information from health care centres was not always available but based on historical information form the mothers.

Conclusion

In SA a significant number of patients with biliary atresia present late for management. Although KPE may be offered successfully to a small number of late presenters, the majority progress to cirrhosis, portal hypertension and ultimately death.

Factors responsible for delay in diagnosis were identified at parental as well as all levels of health care. The study emphasizes the importance of educating the community and medical personnel of the necessity for early referral of a cholestatic child. Information could be disseminated via means of didactic lectures, educational posters, medical management algorithms, stool charts in the "Road To Health Booklet" and establishment of a South African BA national registry. By improving awareness of BA, we ultimately hope to improve prognosis of the condition and encourage Department of Health to institute policies for screening of BA.

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TABLES

Table 1. Age (in days) of all patients with BA

Age (in days)	All patients	Early (<90days)	Late (<90days)
	Median age: 82 days (51;166)	Median age: 52 days (36.0; 68.0)	Median age: 172 days (119.5; 193.5)

Table 2. Demographics of all the patients with BA

SEX	All patients	< 90 days	> 90 days	P Values
M (n)	42	25	17	
F (n)	60	28	32	P =0.28
M:F	1:1.43	1:1.12	1:1.88	

PROVINCE	Overall	< 90 days	> 90 days	P values
Gauteng	76	44	32	
Other SA province	25	9	16	P=0.09
Other country	1	0	1	

Table 3. Maternal Education of all children presenting with BA

Highest achieved	Early	Late
Basic education (Grade 12 or less)	8	12
Basic degree	1	2
Diploma	1	0
National certificate	0	0
Post graduate (Honors)	0	0
Master's Degree	0	0
PHD	0	0
No education	0	0

NB: only have data in 23 patients out of the 102

Table 4. Presenting features in children with biliary atresia

History		Early presenters:53 Number (%)	Late presenters:49 Number (%)	P values
Clinical symptoms	Yellow discoloration	53 (100%)	49 (100%)	
	Fever	1 (2%)	3 (6%)	
	Increasing bilirubin	4 (8%)	2 (4%)	
	Abdominal distension	3 (6%)	10 (20%)	0.036*
	Poor feeding /weight gain	1 (2%)	5 (10%)	0.12
	Other	1 (2%)	7 (14%)	
History of stool colour	Yellow	7 (13%)	16 (33%)	0.019*
	White	42 (79%)	24 (49%)	0.0028*

	Unknown	4 (8%)	9 (18%)	
History of urine colour	Light	6 (11%)	6 (12%)	
	Dark	23 (43%)	19 (39%)	
	Unknown	24 (45%)	24 (49%)	
Examination				
Growth Parameters: median (IQR)	WFA >-2 -2- -3 <-3 unknown	-1.47 (IQR -0.73; -3.10) 32 (63%) 6 (12%) 13 (25%) 2	-2.19 (IQR -1.04; -3.02) 22 (46%) 14 (29%) 12 (25%) 1	0.156
	HFA >-2 -2- -3 <-3 Unknown	-1.00 (IQR 0.27; -2.13) 30 (67%) 9 (20%) 6 (13%) 8	-2.15 (IQR -0.96; -3.64) 20 (47%) 8 (19%) 15 (35%) 6	0.035*
	WFH >-2 -2- -3 <-3 unknown	-1.04 (IQR 0.67; -2.71) 29 (64%) 9 (20%) 7 (16%) 8	-0.72 (IQR 0.29; -2.53) 29 (67%) 6 (14%) 8 (19%) 6	0.632
Clinical signs	Jaundice	53 (100%)	49 (100%)	
	Hepatomegaly	51 (96%)	49 (100%)	
	Splenomegaly	28 (53%)	44 (90%)	0.000*
	Ascites	5 (9%)	11 (22%)	0.101
	Encephalopathy	1 (2%)	0 (0%)	
	Bleeding	0 (0%)	2 (4%)	
	Sepsis/UTI	1 (2%)	2 (4%)	
	Stool colour - pigmented - acholic - unknown	 2 (4%) 31 (59% 20 (38%)	 2 (4%) 27 (55%) 20 (41%)	
	Urine colour -dark -pale -unknown	 15 (28%) 2 (4%) 36 (68%)	 16 (33%) 1 (2%) 32 (65%)	
	Clubbing	1 (2%)	12 (25%)	0.000*
	Pruritus	0 (0%)	3 (6%)	
	Rickets	5 (9%)	13 (27%)	0.036*

WFA- Weight for age, HFA- Height for age, WFH- Weight for height, IQR-Interquartile range, UTI- Urinary tract infection

*p<0.05 comparing early versus late presenters with BA. (Missing p values could not be calculated due to closeness of numbers)

Table 2. Surgical referral and management in 19 children with late presentation biliary atresia (Median follow up 11 months (0; 53)

Surgical Management of late presenters		Number (n)/ Total number (49) n (%)
KPE	Total	10 (20.4%)
	Functioning	2*(10%)
	Partially functioning	4 (40%)
	Non functioning	3 (30%)
	Demised post-surgery	1 (10%)
Laparotomy only, no KPE	Total	3 (6.1%)
Liver Transplantation	Total referred for liver transplantation	6 (12%) (no KPE)
	Transplanted (LDLT)	1 (17%)
	On active list	1 (17%)
	Demised on active list	3 (50%)
	Worked up awaiting listing	1 (17%)

* 1 patient underwent KPE at 99 days and 1 patient at 109 days

KPE=Kasai hepatoportoenterostomy, LDLT= Living donor liver transplant

APPENDIX A: PROTOCOL

LATE PRESENTATION BILIARY ATRESIA AT THE CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

A RESTROSPECTIVE STUDY

DR REFILOE RELEBOHILE MOREKE

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GLOSSARY

BA	Biliary Atresia
LFT	Liver function test
GGT	Gamma-glutamyltransferase
KPE	Kasai Portoenterostomy
CHBAH	Chris Hani Baragwanath Academic Hospital
PGHNU	Paediatric Gastroenterology and Hepatology Nutrition Unit
TEBIDA	N-tert-butyliminodiacetic acid

BACKGROUND

Biliary atresia (BA) is a destructive inflammatory obliterative cholangiopathy of neonates that affects varying lengths of both intrahepatic and extra hepatic bile ducts. If untreated, progressive liver cirrhosis leads to death by age 2 years.(1) The disease is classified according to the level of most proximal biliary obstruction. BA type 1 (about 5%of cases) has luminal patency down to the common bile duct and proximal cystic biliary duct. Type 2 (about 2%) has patency to the level of the common bile duct. Type 3 (>90%) is where the most proximal part of the extrahepatic biliary tract within the porta hepatis is entirely solid.(2)

BA is a rare disorder, with the most accurate estimates of national prevalence from the UK and France ranging from 1 in 17000-19000 live births. It is most common in East Asian countries, with a reported frequency in Taiwan of about 1 in 5000. It is also more common in females than in males. There are limited studies in Africa. In 1998, preliminary data from CHBAH in Soweto estimated the local incidence to be between 1 in 2500 to 1 in 8000 live births (3). Evidence of classic genetic inheritance is scarce. Up to 20% of all cases are associated with other congenital anatomic abnormalities. The most common is BA splenic malformation syndrome, reported in about 10% of European and US series, including polysplenia (90%), situs inversus (50%), and unusual vascular anomalies such as absence of an inferior vena cava and a pre-duodenal portal vein. In the remaining 80% of neonates, BA seems to be an isolated finding. The theory in these neonates is that the pathological obliterative process begins later (perhaps in the perinatal period) than it does in those of syndromic origin (begins in the embryonic phase).

Although the cause and pathophysiology of BA is largely unknown, it can be multifactorial in nature and has a common endpoint of an obliterative cholangiopathy. Some factors that might contribute to development are genetic (polymorphisms might exists that lead to susceptibility to development of inflammation and fibrosis in the affected liver), infective (perinatal hepatotoxic viruses, but no single agent has been identified as causative), inflammatory (possible immune dysregulation and up-regulation of pro inflammatory genes) and even toxic insult.

Typically BA presents shortly after birth with persistent jaundice, dark urine and pale stools.(4) Infants with BA are typically full term and may manifest normal growth and weight gain during the first few week of life. Hepatomegaly may present early, and the liver is often firm or hard to palpation. Splenomegaly is common, and an enlarging spleen suggests progressive cirrhosis with portal hypertension. Direct hyperbilirubinemia (defined as any level exceeding either 2mg/dL or 20% of total bilirubin) is always an abnormal finding and may present from birth, therefore BA should be considered in all neonates with direct hyperbilirubinemia. Early diagnosis is essential, because of the need to implement early surgical intervention and thus investigation of infants with direct hyperbilirubinemia is designed to identify BA and to exclude other causes.

Liver function tests are abnormal with a conjugated hyperbilirunaemia and the GGT is usually higher in BA than in other causes of neonatal cholestasis and serum cholesterol might

be raised. An abdominal ultrasound shows an enlarged liver and typically shows an absent or rudimentary gall bladder after a 4 hour fast. Radioisotope excretion studies, e.g. with a TEBIDA scan typically shows good hepatic uptake but absent or reduced excretion into the intestine within 24 hours. Unfortunately this result is not specific for BA and may be reported positive in children with severe intrahepatic cholestasis such as Alagille's syndrome. Liver histology obtained by percutaneous biopsy is the usual diagnostic method of choice and typically provides evidence of extra-hepatic biliary obstruction by varying degrees of portal tract fibrosis, bile ductular proliferation and cholestasis.

No primary medical treatment is relevant in the management of BA, once BA is suspected; surgical intervention is the only mechanism available for definitive diagnosis (intraoperative cholangiogram) and therapy (Kasai Portoenterostomy). KP and liver transplantation remain the cornerstone of treatment in children with BA. KP can achieve complete clearance of jaundice, restore excretory and synthetic liver function, and enable healthy growth and development, although this outcome is neither certain nor predictable from the outset. KP involves excision of the entire extra-hepatic biliary tree so that the porta hepatis is transected at the level of the liver capsule and the ductules that remain are exposed. A jejunal Roux loop is anastomosed to the cut surface, thus completing the reconstruction.

Success of the KP is measured by clearance of jaundice and is defined as achievement of a normal bilirubin concentration within 6 months of the procedure. Several factors affect the success of this surgery including age at surgery; extend of liver damage and experience of the Centre in which the surgery is done. Numerous studies have shown better surgical outcome in patients younger than 60 days old at the time of surgery, however the optimal timing of the surgery remains controversial.(5) The prognosis for patients aged >3 months at the time of surgery is generally poor. Studies have shown that prognosis is generally better in patients aged <90 days at the time of surgery. Therefore it is crucial that in our limited resource setting, we try and diagnose BA early and refer our patients for KP early.

Many patients are still presenting to hospital after 3 months of age. The aim of my study is to determine how many of the total number of patients that have seen at the CHBH Paediatric Gastroenterology and Hepatology Nutrition Unit (PGHNU) with BA presented late and determine some of the reasons for the late referral in our population. Hopefully the results of my study can be used in future to increase awareness of BA and aid in the development of a screening test for BA for early diagnosis and referral. Some of the reasons for the late diagnosis and treatment reported in other studies include: failure of the patient's parents to attend any form of health check regarding persisting jaundice, parents refusing hospital treatment, repeated reassurances by primary health care workers, significant delay in referral by the general practitioner, misdiagnosis in the referring hospital and in some patients, the initial diagnostic liver biopsy not being interpreted as BA. (6, 7, 8) Studies from the rest of Africa confirm late presentation and lack of facilities to make early diagnosis. (9)

The current proposed screening method for biliary atresia is the use of a stool colour card which the parents or caregiver can use to compare the baby's stool with(10). This stool colour

card has been used in Japan since the 1990's and there have been pilot studies in Taiwan to look at its efficacy (11).

KP is a palliative procedure and does not cure BA. The disease progresses in 70% of children in whom bile drainage is established, with development of fibrosis, portal hypertension and cirrhosis. Despite this fact, more than 80% of those who have had a successful procedure survive longer than 10 years with their native liver with good quality of life. Indications of liver transplant depend on the success of the KP and the rate of development of complications. In infants in whom bile drainage is not achieved, transplantation is usually indicates within 6 months to 2 years of age. Part of my study will also be documenting management of the late presentation BA's.

AIMS AND OBJECTIVES

Primary objectives

- Determine the total number of patients with BA seen at the Chris Hani Baragwanath Academic Hospital Paediatric Gastroenterology, Hepatology and Nutrition Clinic between January 2010 and December 2015 and the number of late presentations
- Identify factors that may be contributing to the late referral
- Determine the presenting features and compare them between early and late presenters
- Document the management of the late presenters
- Document the outcomes of the late presenters

METHODS

- **Study design**

A retrospective, descriptive study will be done. The study will be a review of medical records of infants and children with Biliary Atresia presenting to CHBAH Paediatric Department, between January 2010 and December 2015.

- **Sample population**

  - The sample population will include all patients diagnosed with Biliary Atresia at CHBAH Paediatric Department between January 2010 and December 2015. The estimated sample size of patients with BA for the study is about 120, with about 40% expected to be late presenters. As this is a retrospective study, no informed consent from the study participants' parents will be obtained.

- **Inclusion criteria**

  - Patients with Biliary Atresia confirmed by liver biopsy and/or laparotomy or intra-operative cholangiogram
  - Presentation at CHBAH Paediatric Department between January 2010 and December 2015

- **Exclusion criteria**

  - Any patient whose records do not have adequate data to calculate age at presentation and patients with other missing data may be excluded from part of the analysis

- **Data collection**

Records of all patients with Biliary Atresia will be reviewed and patients that meet the study criteria will be included in the study. The data will be collected and entered onto a prepared data sheet.

Variables measured

All variables measured will be accessed using the Chris Hani Baragwanath Paediatric Gastroenterology Hepatology and Nutrition Clinic database and NHLS laboratory records. The data sheet will capture demographic data, information on patient contact with health care professionals, history of referral, presenting history and clinical features as well as management. (See Appendix A).

- **Data Analysis**

Data collected will be entered into a Microsoft excel spreadsheet and basic statistical analysis will be performed using Microsoft Excel. Appropriate descriptive statistical analysis using percentages and means or medians will be used. Continuous data will be presented as medians with first and third interquartile (Q1 to Q3) or means with standard deviations, depending on the distribution, and categorical data will be presented as percentages. All statistical assessments will be considered significant for a p-value below 0.05. For more detailed statistical analyses, a statistical program such as Statistica will be utilized. In case of unavailable data, participants may be excluded from being part of the analysis.

- **Outcome**

The work will be submitted for a MMed thesis. The results will later be made available to peers through conferences and publications, aiming to increase awareness of the condition and ultimately improve outcome. We're hoping the study will drive an initiative towards

implementation of screening programs for Biliary Atresia in South Africa and make local clinics and level 1 and 2 hospitals aware of the need for early referral of Biliary Atresia for the best possible outcome of treatment.

- **Limitations**

The study is a retrospective study and therefore study data will be collected from an existing database. In case of unavailable data, participants will have to be excluded from part of the analysis.

- **Funding**

I, the researcher, will be responsible for all the funding of this dissertation, which includes mainly the use of stationary and printing. The estimated cost is R400.

- **Ethical considerations**

As this is a retrospective study, no informed consent from the study participants' parents can be obtained. However, confidentiality will be maintained, as all recorded data will remain anonymous. No names, hospital or ID numbers, home address or any other data that would lead to patient identification will be captured. As this is a retrospective record review, no additional study investigations, inconvenience or risk is involved for the participants. The protocol will be submitted to the CEO of CHBAH for permission to conduct this research and Human Research Ethics Committee of the University of the Witwatersrand for approval.

I.TIMELINE

	Jun	**Jul**	**Aug**	**Sep**	**Oct**	**Nov**	**Dec**	**Jan**	**Feb**	**Mar**	**Apr**	**May**	**Jun**	**Jul**
Literature Review														
Preparing Protocol														
Protocol assessment														
Ethics application														
CHBAH application														
Collecting Data														
Data Analysis														
Writing up proposal														
Writing up dissertation														

APPENDIX B: DATA CAPTURING SHEET

Demographics							
Study Case Number							
Sex	**Race**		**Residence**	JHB/Soweto	Gauteng	Other province	Other country
Place of residence	Informal	RDP Home	House	**Maternal Education** Highest level achieved			
Referral To CHBAH	Self	Clinic	Hospital	Private	Other		
Age			<59 days	60-89 days	90-120 days	>120 days	
Date first seen at CHBAH							
Reason for referral							
History:							

	Yellow discolouration Date :		Fever	Rising bilirubin			Abdominal distention
	Poor feeding/ weight gaining			Other			
Stool Colour	Pigmented	Acholic :Date	Unknown	Urine colour	Light	Dark Date :	Unknown
Feeding	Breast milk	Formula	Mixed		Unknown		
Clinical:							
Growth parameters (z scores)	Weight		Height		Weight for height		
Clinical presentation:	Jaundice	Hepatomegaly	Spleen		Ascites	Encephalopathy	
	Bleeding	Sepsis/ UTI	Stool colour		Urine colour	Other:	
Delay in diagnosis >90 days	Yes		No				
Reasons:							
Parental	Delay in presentation "normal"	RHT	No FU		Failure to present PHC		
Primary Health Care clinic	False reassurance	Stool / urine not seen	No FU	Misdiagnosis	Failure to refer hospital		
District hospital services	Failure to investigate /act on results	Unnecessary investigations	No FU	Misdiagnosis	Failure to refer tertiary		
Tertiary hospital services	Liver bx inconclusive	Delay in surgery	No FU	Misdiagnosis	Failure to refer for op		
Blood investigations (CHBAH)							
Date	WCC	Hb	Plat	INR			

Date	TB	DB	TP	ALB	ALT	AST	ALP	GGT	CHOL
A									

Post KPE									

Final Management	Medical:			Surgery: Date						
	Late	RHT	Other	KPE			Lap only No KPE	Liver Bx	Liver Transplant	
				Success	Partial	Failed			Refer	Done

Appendix C: Turnitin Report

Submission date: 09-Sep-2019 04:25PM (UTC+0200)
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of improving outcomes in children with BA. The current screening method for BA in other countries, is the use of a stool colour card which the parents or caregiver can use to compare the baby's stool with [7] This stool colour card has been used in Japan since the 1990's and there have been pilot studies in Taiwan and Switzerland investigating its efficacy. [6]

Objectives

The main objective was to determine the prevalence of patients with late presentation BA (>90 days of age) seen at the CHBAH PGHNU between January 2010 and December 2015 and attempt to identify factors that might have contributed to the late referral or presentation. Secondary objectives included documenting the management and outcomes of the late presenters and comparison of the clinical characteristics at first presentation, between early presenters (≤90 days of age) and late presenters.

Methods

A retrospective analysis of all children with BA that presented at the CHBAH between January 2010 and December 2015 was undertaken. Data were obtained from the CHBAH PGHNU clinical records and database and extrapolated onto a prepared data collection sheet. The data sheet captured demographic data, information on patient contact with health care professionals, history of referral, presenting history and clinical features, on all patients diagnosed with BA during the study period. Growth parameters were documented using WHO arthroplus as part of clinical assessment. Management and outcome were documented on late presenters.

Early presentation was defined as presentation at ≤ 90 days of life, while late presentation was presentation at > 90 days of life. Management was divided into medical alone or combined medical and surgical management. Surgical management was subdivided into laparotomy only or laparotomy with KPE. The small number of late presenters who underwent KPE were documented as having a functioning, partially functioning or non-functioning KPE (icteric with acholic stool) at 3 months and 6 months post-surgery. Outcomes recorded included whether patients were still alive at the end of the study, follow up period with their native liver and the number referred for liver transplantation. The cut off for follow up for the late presenters was set as 31st January 2017. Patients who were lost to follow up were censored at the time of their last visit.

Data collected was entered into a Microsoft excel spread sheet and basic statistical analysis performed using Microsoft Excel. Appropriate descriptive statistical analysis using percentages and means or medians were used. Continuous data has been presented as medians with first and third interquartile (Q1 to Q3) and categorical data presented as percentages. All statistical assessments were considered significant for a p-value below 0.05. For more detailed statistical analyses, a statistical program SPSS was utilised. In case of unavailable data, participants were excluded from being part of the analysis.

Ethics permission was obtained from the University of the Witwatersrand (Wits)'s Human Research Ethics Committee (Medical) (ref.no.M160967)

Results

There were 122 patients with BA seen at the CHBAH PGHNU between January 2010 and December 2015. Of the 122 patients seen, 13 were excluded from the study due to inadequate data and only 102 patients were then eligible for inclusion into the study. Of the 102 patients, 53 (52%) were early presenters and 49 (48%) were late presenters. The median (IQR) age at presentation for all 102 patients was 82 days (51;166) as compared to median age of 172 (193.5; 119.5) for the late presenters.

Demographics:

Of the 102 patients, 76 (74.5%) were from Gauteng province, with 28 of those from the Johannesburg/Soweto area. There were 42 males and 60 females with a male: female ratio of 1:1.43 (p value 0.28) and the majority of the patients were black (97%) a reflection of the population demographics seen at CHBAH. Of the 102 patients, data on highest level of maternal education were only available on 24 mothers (10 early presenters and 14 late presenters). Of these 24, 20 mothers had achieved only basic education (grade 12 or less), 1 mother had a diploma and 3 mothers had a university degree. There was inadequate data to extrapolate whether maternal education played a role in late presentation.

Clinical signs and symptoms: early vs. late presenters

The presenting features and clinical presentation of the 102 patients with BA are shown in Table 1. History of stool colour was documented in 89 patients, but only confirmed on examination in 62. Of note, there were a significant number of patients whose stool and urine colour was not examined despite the presence of jaundice. The only statistically significant growth parameter between the two groups was height for age (stunting).Significantly, a greater number of mothers reported acholic stools in the early presenters as compared to the late presenters. As expected splenomegaly, digital clubbing and clinical evidence of rickets were significantly more prevalent in the late presenters with a more chronic form of the liver disease.

Factors contributing to late presentation:

A combination of factors contributed to the late presentation in the majority of patients. Reasons for late presentation were available in 47 of the 49 patients. Preference of traditional medication use, or reluctance for surgical intervention was not given as factors in any of the patients.

Documented reasons for late presentation included:

1) Parental factors: 20 mothers thought the jaundice was normal, 6 failed to ever present to a primary health care facility and 4 defaulted follow up appointments
2) Medical factors:
   -Primary health care facilities: 15 patients were given false reassurance (jaundice assumed to be due to physiological jaundice or breastfeeding jaundice) and 3 although not referred were given follow up appointments for review.
   -District hospitals: 4 patients were seen at the district hospitals and not referred to a tertiary centre: 1 was misdiagnosed as sepsis, treated and discharged, 1 was falsely reassured and not investigated, 1 was investigated but no action was taken on abnormal laboratory results and 1 patient was given a follow up appointment for review.

-Tertiary centre: 1 patient was diagnosed with an Escherichia Coli urinary tract infection, and the underlying BA was missed and confirmed at a later presentation.

Management and outcomes of the late presenters

Thirteen patients were referred for KPE (Table 2). Macroscopically cirrhotic livers noted at time of laparotomy precluded performance of KPE in 3 patients. KPE was performed on 10 patients, and the median age at KPE was 112 days (120.75; 105.25). Early resolution of jaundice defined as achieving bilirubin levels less than 34µmol/L by 6 months post-surgery was achieved in 2 of the 10 patients. 4 were partially functioning (icteric with pigmented stool), and 3 were non-functioning (icteric with acholic stool).

The median follow up for the late presenters was 11 months (0; 53). By 6 months post first presentation, 28 (57.1%) patients were still alive, 14 (28.6%) were already lost to follow up and 7 (14.3%) were known to have demised. By 12 months: 19 (38.7%) patients were still alive, 20 (40.8%) were lost to follow up, 9 (18.4%) were known to have demised and 1(2.1%) referred to private health care.

As at 31st January 2017, 10 (20.4%) patients were still alive and 12 (24.5%) confirmed to have demised. Documented causes of death included: 1 due to post-operative complications, 1 due to advanced retro viral disease, 1 due to upper gastro intestinal tract bleed, and in 9 patients, causes were unknown. Two patients were referred to private health care and their outcome was unknown, 9 patients never made it to any follow up appointments post discharge and are presumed to have demised and 16 patients were initially followed up, but discontinued clinic attendance at varying time intervals and were also presumed to have demised. Based on documented Wits Donald Gordon Medical Centre transplant data, none of the defaulters were transplanted up to the last follow up period.

Discussion

The incidence of biliary atresia in black infants in South Africa may be among the highest in the world, and the survival rates are poor as compared to more affluent countries. In developed countries, 5 year native-liver survival rates of up to 60% have been reported [19], whereas a local study has shown a 2 year native liver survival rate of 19 %.[12] The majority of patients are from poor socio economic backgrounds with difficulties in accessing health care services and often relying on primary health care services to refer them to a tertiary level hospital should the need arise. Late presentation BA is a problem in South Africa. Children with BA present late, with more than a third not able to receive KPE due to late presentation and established cirrhosis [11] and confirmed by our study where nearly half of our patients were late presenters. The etiological heterogeneity of BA is complex. Timeous diagnosis and referral will be one of many factors that would need to be addressed to ultimately improve outcomes in children with BA.

Many studies have been performed to determine the factors that may influence the surgical outcomes of a KPE, and a lot of attention has been paid to the age at the time of the operation which was reported as a significant risk factor by Kasai and local studies. He reported a better surgical outcome in patients younger than 60 days old at the time of surgery.[8] The optimal timing of KPE remains controversial.[4,5] Although the prognosis for patients aged ≥3 months is generally poor, there is no consensus whether 2 months of age is a critical age for surgery that

can impact the prognosis.[13] KPE has been known to be performed in children more than 60 days or even up to 100 days suggesting that referring for surgery should be based on an individual basis and clinical picture. [5, 15] Two of our patients that were more than 90 days old at presentation had complete resolution of jaundice. This helps bridge the gap between diagnosis and delay referral for liver transplant, as the study has shown that patients can still benefit from KPE at an older age.

Malnutrition is a significant clinical problem in children with BA, particularly in the first year of life and has been shown to increase morbidity and mortality risk post KPE and liver transplantation. [11] Assessment of nutritional status in patients with chronic liver disease is difficult and imprecise. This is because indicators of nutrition on assessment are confounded by the presence of significant visceromegaly, oedema and ascites. Body weight alone can result in erroneous representation of nutrition in these patients. This might explain why the only growth parameter that was statistically significant was height for age (stunting). Mid upper arm circumference (MUAC) and triceps skin fold are more reliable representations of nutritional status in these children but were not documented in the study population and should be used more often. Special emphasis should be placed on nutritional rehabilitation to ensure better outcomes in the late presenters who turn to be significantly malnourished as compared to the early presenters.

Although yellow discoloration of the skin and conjunctiva was present in all patients, this did not necessarily translate into early presentation or investigation and referral. The rapid progression of this condition was reflected in the clinical differences between the two groups. Splenomegaly, clubbing and rickets, signs of chronicity, were significantly different between the 2 groups. The presence of pale stools is a sensitive marker for cholestatic liver disease, but parental reports of the history of pale stools can be misleading. [18] Of note, more parents in the early presenters group complained of pale stools as compared to the late presenters group. Stool colour should be assessed in all patients presenting with prolonged jaundice to assist in the diagnosis of BA. On clinical examination, 40 of the 102 did not have their stool examined at diagnosis by the admitting doctor. Stool colour charts (showing different normal and abnormal stool colours to be compared with baby's stool), which have been used successfully in Taiwan since 2004 [7], could either be placed inside the road to health booklets or posters with the same stool colour charts could also be displayed in waiting rooms in the clinics or secondary level hospitals. The UK introduced the 'yellow alert', an educational program aimed at expediting the referral of jaundiced patients to tertiary centres for investigation and treatment if required. [10] A similar approach can also be undertaken by ensuring that algorithm posters regarding management of a child with jaundice are available in PHC to ensure early detection and referral of cholestatic children.

Based on various local studies, it has been documented that late presentation is a problem in RSA. [2, 12] Our study identified a number of factors that contributed to the delay in presentation. These included parental reasons and health care worker related reasons. The study attempted to correlate maternal education with delayed presentation, however due to limited data, a conclusive correlation could not be made. Emphasis should be placed on educating not only the community but health care workers as well of the significance of persistent jaundice, of more than 2 weeks duration, inspection of the stool colour, that would promote early identification of the condition and expedite referral for better outcomes. DHS and tertiary hospitals need to be

aware that sepsis may present as cholestatic jaundice, and should always consider an underlying liver pathology predisposing the child to sepsis. Therefore they need to monitor liver functions post discharge and ensure normality.

The majority of children with suspected established cirrhosis were excluded from surgical intervention as offering KPE to these children was unlikely to result in successful outcome. Only a small percentage of late presenters had successful KPE, leaving a large number of patients which should have been ideally referred for liver transplantation. However, liver transplant still remains a very scarce resource in South Africa and only available to a small percentage of our patients with BA. [14, 15] Some of the reasons for non-referral include: poor socio-economic circumstances, lack of accessible transport, delays in diagnosis and limited remuneration from the National Department of Health. There are only two centres in South Africa that offer paediatric liver transplantation services, one at the Red Cross War Memorial Children's hospital in Cape Town where liver transplants have been performed since 1991 [16] and one at Wits Donald Gordon Medical Centre in Johannesburg (WDGMC) which has been performing liver transplants since 2005. [16, 17] In this study, only 6 of the late presenters were referred for transplant at the WDGMC. At the time of the study, mostly cadaveric livers were available for transplantation which limited availability of livers for transplantation. However since then, the availability of living related donor transplantation (LRDT) has led to many more referrals and the increase in transplants done.

Long term outcomes were only available in a small percentage of the late presenters as a large number defaulted follow up appointments, or never presented for their follow up appointments since discharge and have been presumed demised. Reasons for the poor follow up include low health literacy and the inability to obtain transportation to appointments. Therefore improving patient health literacy and education may help empower patients to make better care decisions such as attending follow up appointments. To our knowledge and based on the transplant centres data, those who defaulted follow up did not receive a liver transplant, so are presumed to have demised.

Limitations

The study is a retrospective study and therefore data was collected from an existing database. In case of unavailable data, participants were excluded from part of the analysis. In view of a high attrition number in follow up appointments, confirmed outcomes for the late presenters were available in a minority of the patients with majority assumed to have demised. Lack of details regarding direct causes of death in the patients that were known to have demised was also a limitation. Direct clinical information from health care canters was not available but based on historical information form the mothers, in a number of patients.

Conclusion (look at conclusions in the abstract and introduction to correct)

BA carries a poor prognosis if not surgically corrected especially in developing countries. The majority of patients demised, without surgical intervention within the first 2 years of life, in

Conclusion (look at conclusions in the abstract and introduction to correct)

BA carries a poor prognosis if not surgically corrected especially in developing countries. The majority of patients demised, without surgical intervention within the first 2 years of life, in keeping with previous documented studies. We feel the study could be the basis for evidence based medicine to encourage change in the DOH policies. Although KPE outcomes are not comparable to the rest of the world and only a small percentage are successful, as compared to more affluent and well-resourced countries. However, in late presenters it still gives an opportunity to achieve bile drainage with their native liver survival. A significant number of patients (48%) with biliary atresia presented late for management. Although KPE was offered to a small number of late presenters, the majority progressed to cirrhosis, portal hypertension and ultimately death.

Factors responsible for delay in diagnosis were identified at parental as well as all levels of health care. The study emphasizes the importance of educating the community and all health care workers of the necessity for early referral of a cholestatic child. We hope the study will help improve awareness and screening of BA.

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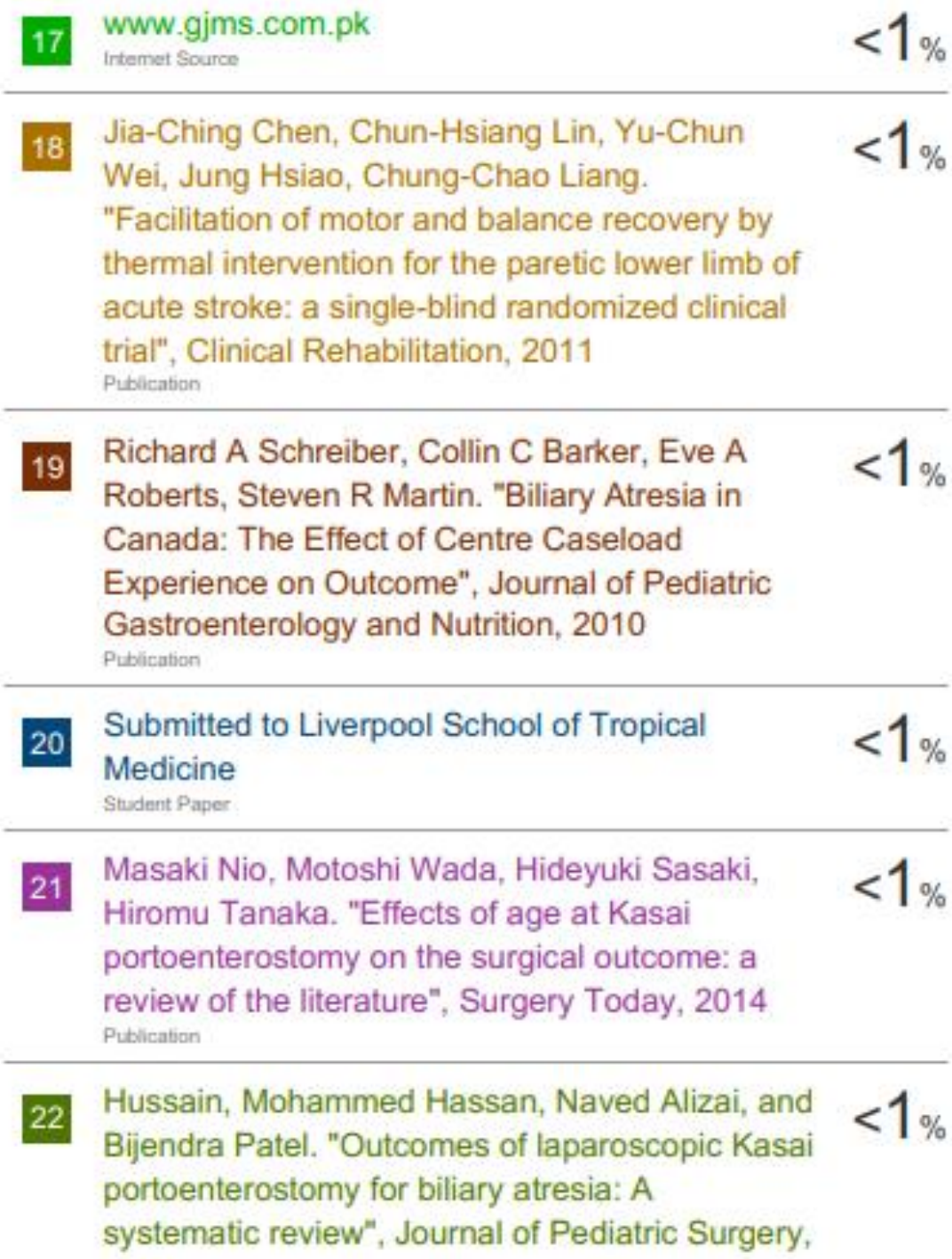

Appendix D: Plagiarism declaration

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS, SENATE PLAGIARISM POLICY:

I……, student number……, am a student registered for the degree of ……..in the academic year. I hereby declare the following:- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong. – I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise. – I have followed the required conventions in referencing the thoughts and ideas of others. – I understand that the University of the Witwatersrand may take disciplinary action against me if there is s belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing. – I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature:…….. Date:…….

Appendix E: Ethics clearance

R14/49 Dr Refiloe Moreke

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160967

NAME: (Principal Investigator)	Dr Refiloe Moreke
DEPARTMENT:	Paediatrics Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Late Presentation Biliary Atresia vs Total Number of Biliary Atresia's seen in the Past 5 Years at the Chris Hani Baragwanath Hospital
DATE CONSIDERED:	30/09/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Christina Hajinicolaou
APPROVED BY:	Prof A Woodiwiss, Co- Chairperson, HREC (Medical)
DATE OF APPROVAL:	12/12/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in September and will therefore be due in the month of September each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix F: Certificate of submission signed by student

CERTIFICATE OF SUBMISSION FOR EXAMINATION OF MASTERS RESEARCH REPORT / DISSERTATION OR PHD THESIS SIGNED BY HIGHER DEGREES CANDIDATES

Full name			
Student number			
Title of submitted Research Project: _____ _____ _____ *NB: If this title is different to your previously approved title, no further action can be taken by the Faculty Office until a change of title has been approved.*			
Contact no		E-mail	

1. If you are likely to move in the next 6-12 months, please give the anticipated date of move: _____
2. I hereby submit my **Masters (research report)** / **Masters (dissertation)** / **PhD thesis for examination**
   (Select whichever is applicable)
3. I have checked all copies of my research report / dissertation / thesis and declare that no pages are missing or poorly reproduced.
4. I have submitted _____ bound copies and _____ copies on CD

5. **I confirm that I have:**
   a) A signed declaration indicating my understanding of the concept of plagiarism and a denial of plagiarism in my research document.
   b) A report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document included as an appendix.

6. **I confirm that I have:**
   a) Not used either human or animal tissue or records **Yes/No**
   b) If yes: I have included the ethics waiver letter pertinent to my research as an appendix **Yes/No**
   c) Done research using animals **Yes / No**
      If yes: I have included a copy of the animal ethics committee clearance certificate as an appendix in this document **Yes/No**
   d) Done research using human subjects, human tissue or patient records **Yes / No**
      If yes: I have included a copy of the human ethics clearance certificate as an appendix to the research document **Yes/No**

7. I understand that I may not graduate unless my University fees have been paid in full.

8. My Supervisor(s) names, departments, telephone numbers and email addresses are as follows:

Name			
Department			
Telephone		E-mail	
Name			
Department			
Telephone		E-mail	
Name			
Department			
Telephone		E-mail	

List all publications, which you have published in peer-reviewed journals from your postgraduate research report/dissertation/thesis during the course of your studies in the Faculty of Health Sciences (Include authors, year, title of paper, name of journal, volume number and page numbers). This information is mandatory.

_____
_____
_____
_____
_____
_____
_____
_____

Signature of candidate: _____ Date: _____

Appendix G: Certificate of submission signed by supervisor

CERTIFICATE OF SUBMISSION FOR EXAMINATION SIGNED BY SUPERVISORS OF HIGHER DEGREES CANDIDATES

Full name	
Student number	

Candidate for the degree of:

_____

has submitted his/her thesis/dissertation/research report

Entitled:

_____

_____

_____

_____

_____

_____

_____

Contact no		E-mail	

Mark with an X on appropriate box	**Yes**	**No**
Has this thesis/dissertation/research report been submitted with the acquiescence of the supervisor?		
To the best of your knowledge are you able to verify that this is the candidate's work, except as otherwise stated by the candidate?		
The substance (nor any part of it) has not been submitted in the past nor is being submitted for a degree in any other university?		
The candidate has acknowledged wherever any information used in the thesis, dissertation or other work has been obtained by him/her while employed by, or working under the aegis of, any person or organization other than the University or its associated institutions?		
Have examiners been nominated and approved?		

I certify that this thesis/dissertation/research report has the approval of the Animal Ethics Committee / Committee for Research on Human Subjects and the Number of the Certificate of Approval is:

_____

List all publications, which your student has published in peer-reviewed journals from his/her postgraduate research report/dissertation/thesis during the course of his/her studies in the

Faculty of Health Sciences (Include authors, year, title of paper, name of journal, volume number and page numbers). This information is mandatory.

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_____

Name of Supervisor 1:

_____

Telephone: _____ Email:

_____

Signature: _____ Date:
_____

Name of Supervisor 2:

_____

Telephone: _____ Email:

_____

Signature: _____ Date:
_____

Name of Supervisor 3:

_____

Telephone: _____ Email:

_____

Signature: _____ Date:
_____

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IMPORTANT NOTICE WITH REGARD TO THE SENATE STANDING ORDERS:

A.22 Submission against advice of Supervisor

If the Supervisor is not prepared to agree to the submission of a thesis, the candidate shall still be entitled, if he or she wishes, to submit it for examination. When a thesis is submitted against the advice of the Supervisor, this should be recorded in the minutes of the Faculty Graduate Studies Committee. In such a case, no internal examiners are appointed but a Supervisor's report will still be required. After the examination process, the external examiner(s) will be advised by the Chairperson of the Faculty Graduate Studies Committee that the thesis was submitted against the advice of the Supervisor.

A.24 *Nomination of Examiners*:

Nomination of examiners should take place at least six weeks before submission of the thesis or dissertation. *(The Postgraduate Office will not accept any submission for examination without the confirmed appointment of the nominated examiners*.)

A.25 Confidentiality of names of examiners (both external and internal)

The names of the examiners should be confidential during the examination process and may only be revealed to the candidate with the acquiescence of the examiner once the final version of the thesis has been submitted to the Faculty and the process has been completed.