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Demographics, aetiology and outcome of paediatric acute liver failure in Singapore

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ABSTRACT

Introduction: The aetiology of paediatric acute liver failure (PALF) varies widely according to age, and geographic and socioeconomic factors. This study aimed to examine the epidemiology, aetiology and outcome of PALF in Singapore at a single centre.

Methods: A retrospective review was performed of patients aged 0–18 years who were diagnosed with PALF from 2007 to 2019. PALF was defined by: absence of chronic liver disease; biochemical evidence of acute liver injury; and coagulopathy, non-correctible by vitamin K, defined as prothrombin time (PT) ≥ 20 seconds or international normalised ratio (INR) ≥ 2.0 regardless of hepatic encephalopathy (HE) or PT ≥ 15 seconds or INR ≥ 1.5 in the presence of HE.

Results: 34 patients were included. Median age at diagnosis was 10 months (range 7 days to 156 months). The top three causes of PALF were indeterminate (41.2%), metabolic (26.5%) and infectious (26.5%) aetiologies. A metabolic disorder was the most frequent aetiology in infants < 12 months (38.9%), whereas an indeterminate cause was the most common in children > 12 months (50%). No cases of viral hepatitis A or B presenting with PALF were detected. Overall spontaneous recovery rate (survival without liver transplantation [LT]) was 38.2%, and overall mortality rate was 47.1%. Six patients underwent living-donor LT, and the post-transplant survival at one year was 83.3%.

Conclusion: The aetiologic spectrum of PALF in Singapore is similar to that in developed Western countries, with indeterminate aetiology accounting for the majority. PALF is associated with poor overall survival; hence, timely LT for suitable candidates is critical to improve survival outcomes.

Keywords: liver failure, paediatric

INTRODUCTION

Paediatric acute liver failure (PALF) is a rare but life-threatening condition characterised by hepatocellular necrosis and rapid deterioration in liver function, with or without encephalopathy, and classically in the absence of pre-existing chronic liver disease.[1] The aetiology of PALF varies widely depending on the age of the child, and geographic and socioeconomic factors. Viral hepatitis A and B are reported to be more common in Asia, particularly in India where hepatitis A infection is a major cause of PALF.[2] By contrast, indeterminate or seronegative, non-A–E hepatitis is the most common cause of PALF in Western populations.[3] Inborn errors of metabolism (IEM) are a commonly identified cause of PALF in young infants and tend to occur at a higher incidence in populations with high rates of consanguinity.[4,5] Interestingly, recent data from the Far East in China and Taiwan has shown that indeterminate aetiology, rather than viral hepatitis, constituted the majority of cases of PALF.[6,7] The prognosis of PALF depends on the age at presentation, underlying aetiology and onset of hepatic encephalopathy (HE). The mortality rate may be as high as 70% without appropriate management and/or liver transplantation (LT).[8]

The medical management of PALF principally entails supportive care, with the priorities focused on prevention and treatment of associated complications, investigation of the cause of liver impairment, and administration of disease-specific treatment if a treatable cause can be identified. Orthotopic LT is a life-saving procedure in fulminant PALF, and one-year post-LT survival rates have improved to over 80%–90% in recent times.[9] Timely referral for transplant assessment is critical, and numerous papers have proposed clinical and biochemical parameters as well as prognostic scores for early prediction of the failure of conservative medical treatment.[1,8,10] In countries with low availability of deceased-donor organs, living-donor liver transplantation (LDLT) has been shown to achieve comparably favourable outcomes in PALF.[9,11,12]

In Singapore, a developed Southeast Asian city-state with a multi-ethnic population of 5.5 million, almost all paediatric LTs performed are LDLT. This study aimed to examine the epidemiology, aetiologic spectrum, survival rate and outcomes of patients with PALF presenting at a single tertiary paediatric centre in Singapore over a 13-year period.

METHODS

This study is a retrospective review of all paediatric patients aged 0–18 years who were diagnosed as having PALF from January 2007 to December 2019 at KK Women's and Children's Hospital, which is the largest paediatric referral centre in Singapore. Cases were searched and identified from hospital medical records by the discharge diagnosis of 'acute liver failure' and 'fulminant hepatic failure'. PALF was adapted from the following criteria set by the PALF study group: (a) absence of chronic liver disease; (b) biochemical evidence of acute liver injury; and (c) coagulopathy non-correctable by vitamin K, defined as prothrombin time (PT) ≥ 20 seconds or international normalised ratio (INR) ≥ 2.0 regardless of the presence or absence of HE, or PT ≥ 15 seconds or INR ≥ 1.5 in the presence of clinical HE.[13] Cases must fulfil all three criteria to be considered for inclusion in the study. Patients with known underlying chronic liver disease or who had previously undergone LT at the time of acute liver failure were excluded. The standard adult HE grading scale was used for children aged three years and above, whereas an adapted HE scale was used for infants and young children below three years of age.[14]

The investigation and management of PALF were carried out in accordance with standard guidelines and tailored according to the age of the patient.[15] N-acetylcysteine was not part of the standard management of non-paracetamol PALF but was used according to the judgement and discretion of the attending gastroenterologist/hepatologist. Aetiologies were classified as

infectious, metabolic, immunologic, toxic/drug, haematologic/malignant and indeterminate based on presenting history, clinical signs and investigation results. Infectious aetiology was defined by detection of a specific hepatotropic virus by positive immunoglobulin M serology, polymerase chain reaction and/or presence of the virus in liver tissue and included but not limited to hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis E virus, herpes simplex virus (HSV), human herpes virus 6 (HHV6), adenovirus, enterovirus, Epstein Barr virus and cytomegalovirus. Cases in which a primary bacterial infection was judged to be the predominant factor leading to PALF were sub-classified as having non-viral infectious aetiology. Metabolic causes, which included IEM and Wilson disease, were suspected based on metabolic abnormalities on appropriate screening tests and/or confirmation of a deleterious mutation in the associated gene(s). Autoimmune hepatitis and gestational alloimmune liver disease (GALD), which is the underlying disorder resulting in the condition that was previously termed as neonatal haemochromatosis (NH), were classified under immunologic aetiology and were defined by the established diagnostic criteria for these conditions.[16,17] Toxic (drug) aetiology was based on the history of ingestion of a substance that was hepatotoxic or in a quantity that was hepatotoxic, and confirmed based on history, blood and/or urine toxicological analysis. Cases were classified as haematologic/malignant if they were confirmed on peripheral blood film, bone marrow examination, tissue biopsy and/or imaging to have an underlying hematologic or non-hematologic malignancy that had resulted in liver failure. Cases with no identified cause despite standard and extended investigations were defined as having indeterminate aetiology.

Primary outcomes examined in the study were spontaneous recovery (survival without LT), LT and death without LT at four weeks from the time of hospital admission. LT assessment, surgery and postoperative care were performed at a separate paediatric liver transplant unit at the

National University Hospital. Data on demographics, clinical presentation, biochemical abnormalities (peak or trough values where appropriate), treatment received, survival outcomes and peri-/post-transplant outcomes was collected and retrospectively analysed. Data analysis was performed using IBM SPSS Statistics for Windows version 19 (IBM Corp, Armonk, NY, USA). Continuous variables were expressed as median (range or 25%–75% interquartile range), and categorical variables were expressed as number (percentage). Comparisons between groups were performed using Mann-Whitney *U* or Kruskal-Wallis tests for non-parametric continuous variables, and χ^2 test or Fisher's exact test for categorical variables. Statistical significance was set at p-value < 0.05. The study was approved by the SingHealth Centralised Institutional Review Board (reference number: 2020/2572).

RESULTS

In total, 34 patients were diagnosed with PALF during the study period; 23 (67.6%) of them were male, and the median age at presentation was 10 months (range 7 days–156 months). Just over half (n =18) of the patients were aged less than 12 months. The age distribution of the patients is depicted in Fig. 1. With regard to ethnic distribution, Chinese formed the largest proportion of patients (n = 19, 55.9%), followed by Malay (n = 7, 20.6%) and Indian (n = 3, 8.8%). Other races constituted 14.7% (n = 5) of cases.

Indeterminate aetiology accounted for the largest proportion of cases in our series (n = 14, 41.2%), followed by metabolic (n = 9, 26.5%) and infectious aetiologies (n = 9, 26.5%). IEM was the most frequent aetiology for PALF in infants younger than 12 months (7 out of 18, 38.9%). These included organic acidaemia (n = 3), urea cycle defect (n = 2) and mitochondrial disorders (n = 2). Metabolic disorders presenting in children above one year of age (n = 2) were Wilson

disease (13 years of age) and mitochondrial disorder (three years of age). The most common aetiology in older children above 12 months of age was indeterminate (n = 8, 50%). Within the group of patients with infectious aetiology, primary viral infections accounted for six out of nine cases, which included enterovirus (n = 1), adenovirus (n = 1), HHV6 (n = 1), parvovirus (n = 1), dengue virus (n = 1) and influenza (n = 1). No cases of PALF relating to HAV or HBV infections were observed. Three patients had non-viral infectious aetiology with culture- or serology-proven bacterial infections that resulted in PALF and multi-organ failure. No patient with autoimmune hepatitis or GALD presented with PALF in our series. Of the two patients who had toxic (drug) aetiology, paracetamol (n = 1) and co-trimoxazole (n = 1) were found to be the offending drugs. Table I summarises the specific causes of PALF stratified by age group.

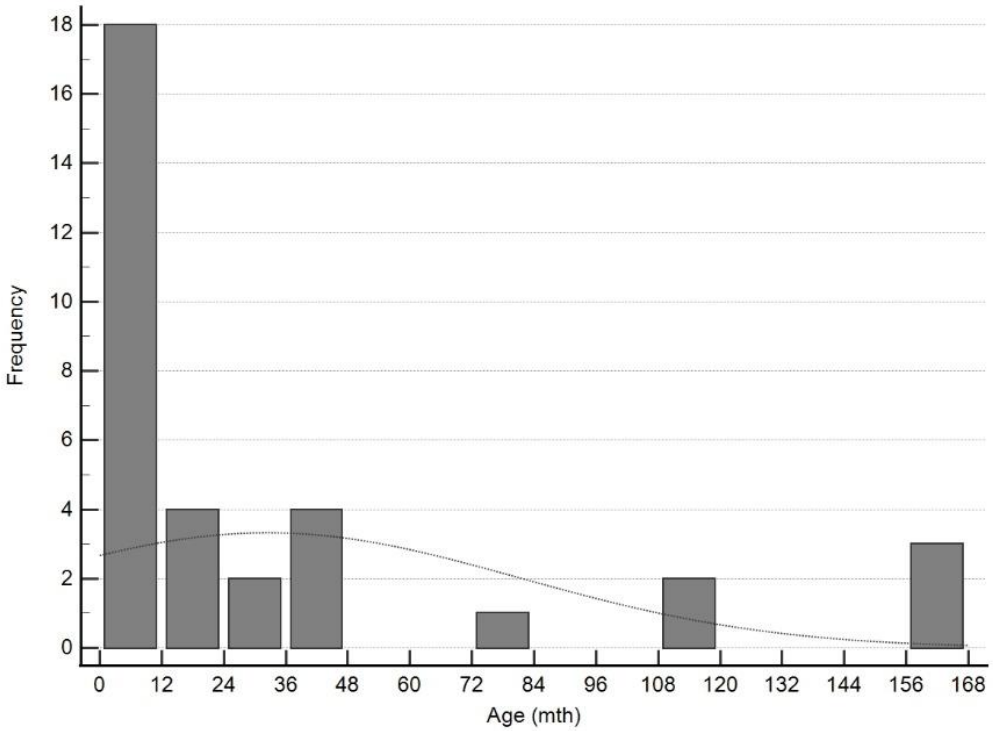

Fig. 1 Graph shows the age distribution of patients with paediatric acute liver failure.

Table I. Aetiology of paediatric acute liver failure (PALF) stratified by age group.

Aetiology of PALF	No. (%)		
	Age ≤ 12 mth (n = 18)	Age > 12 mth (n = 16)	Total (n = 34)
Indeterminate	6 (33.3)	8 (50.0)	14 (41.2)
Metabolic	7 (38.9)	2 (12.5)	9 (26.5)
Infectious	5 (27.8)	4 (25.0)	9 (26.5)
Toxic (drug)	0 (0)	2 (12.5)	2 (5.9)

The most common clinical feature was jaundice (n = 25, 73.5%). HE was documented in 20 (58.5%) patients, half of whom had mild Grade 1 HE (n = 10). The clinical features, complications and laboratory parameters of the patients are summarised in Table II. When laboratory results across the aetiology groups were compared, peak alanine transaminase (ALT) and aspartate transaminase levels were found to be highest in the group of patients with toxic drug as the cause of ALF ($p < 0.001$ and $p = 0.007$ respectively), whereas peak serum lactate was most elevated in metabolic causes of PALF, with this trend approaching statistical significance ($p = 0.08$). No significant difference was observed in other parameters such as serum bilirubin, albumin and ammonia between the different aetiologic groups. Fig. 2 summarises the key laboratory parameters stratified by aetiologic groups.

All 34 patients were managed in the intensive care unit. With regard to requirement of critical care support, invasive mechanical ventilation, inotropic support and renal dialysis were required in 16 (47.1%), 13 (38.2%) and 7 (20.6%) patients, respectively. N-acetylcysteine was used in 27 (79.4%) out of 34 patients, of whom 11 patients had indeterminate aetiology, seven had metabolic aetiology, seven had infectious aetiology and two had toxic (drug) aetiology.

Table II. Overall clinical features, complications and biochemistry of patients with paediatric acute liver failure (n = 34).

Clinical/laboratory parameter	No. (%) / median (range)
Jaundice	25 (73.5)
Ascites	24 (70.6)
Hepatic encephalopathy	20 (58.5)
Grade 1	10 (29.4)
Grade 2	7 (20.6)
Grade 3	1 (2.9)
Grade 4	2 (5.9)
Fever	16 (47.1)
Hepatomegaly	8 (23.5)
Bleeding	6 (17.6)
Rash	3 (8.8)
Seizure	2 (5.9)
Acidosis (pH < 7.3)	15 (44.1)
Hypoglycaemia (blood sugar ≤ 2.5 mmol/L)	12 (35.3)
Total bilirubin (µmol/L)	226 (11–847)
Direct bilirubin (µmol/L)	121 (6–529)
Albumin (g/L)	20 (11–28)
Alanine transaminase (U/L)	1397 (32–11702)
Aspartate transaminase (U/L)	2749 (79–18304)
Prothrombin time (s)	36.4 (20–114.7)
International normalised ratio	4.23 (1.8–17.13)
Ammonia (µmol/L)	109 (29–2118)
Lactate (mmol/L)	5.55 (1.3–23.5)
Creatinine (µmol/L)	47 (26–220)

The overall mortality rate of PALF in our series was 47.1% (16 out of 34 patients). Spontaneous recovery rate was 38.2% (13 out of 34), while six (17.6%) patients underwent LT. 15 (44.1%) patients died without LT; 12 of these had contraindications to LT that included multi-organ failure (n = 7), mitochondrial disorder (n = 3) and ongoing sepsis (n = 2). Transplant-free survival rates were the lowest for metabolic (2 out of 9, 22.2%) and indeterminate (4 out of 14, 28.6%) aetiologies. The outcomes within each aetiologic group are depicted in Fig. 3.

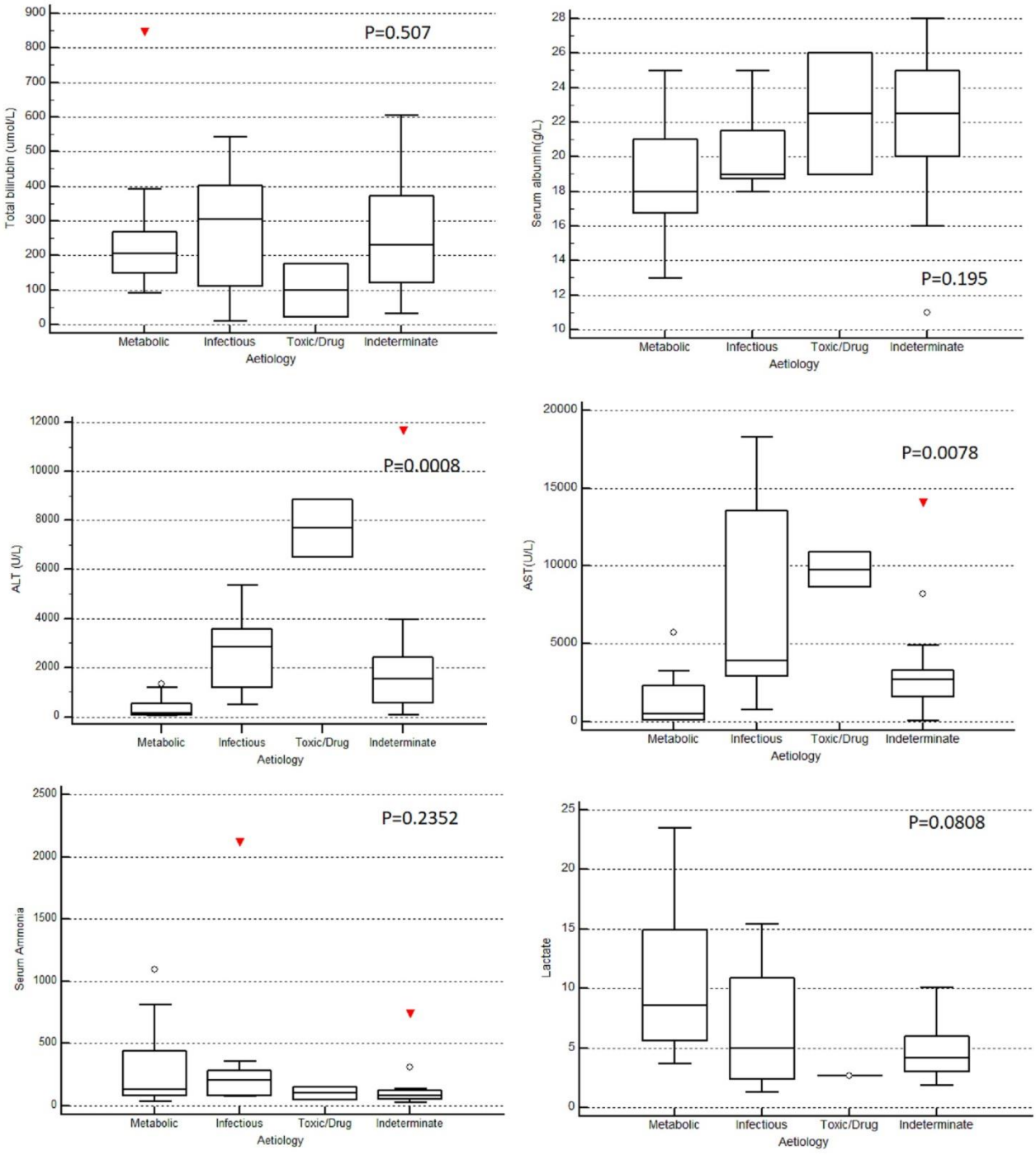

Fig. 2 Box plots compare the serum bilirubin, albumin, alanine transaminase, aspartate transaminase, ammonia and lactate levels among the aetiologic groups.

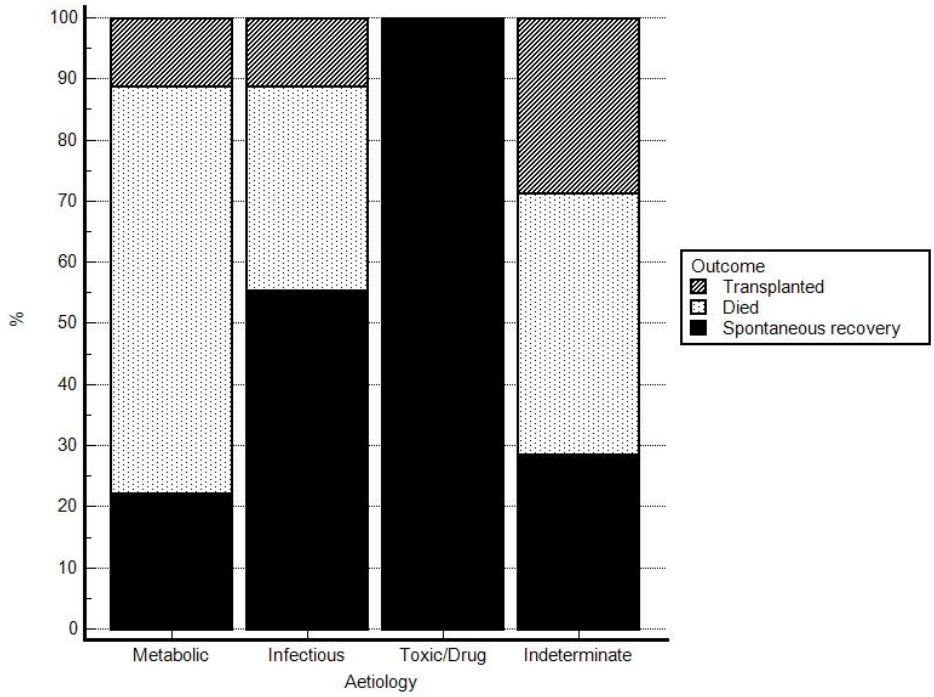

Fig. 3 Graph shows the outcome of paediatric acute liver failure stratified by aetiologic groups.

In total, nine patients were referred and underwent work-up for LT, but three patients (two with indeterminate aetiology and one with IEM) died before LT could be performed. The aetiologies of PALF in the six patients who underwent LT were indeterminate (n = 4), metabolic (n = 1) and HHV6 hepatitis (n = 1). All six patients received living-donor LT, and one-year post-transplant survival of this sub-cohort was 83.3% (5 out of 6). The median age of patients who underwent LT was 117 (range 6–156) months.

A univariate sub-analysis was performed to identify the risk factors for death or the requirement of LT in our cohort of patients with PALF (Table III). Peak serum lactate > 4 mmol/L (odds ratio [OR] 11.7, 95% confidence interval [CI] 1.85–74.19; p = 0.009), INR > 4.0 (OR 4.5, 95% CI 1.02–19.90; p = 0.047), HE (OR 4.0, 95% CI 0.92–17.30; p = 0.064) and need for invasive ventilation (OR 5.42, 95% CI 1.14–25.83; p = 0.034) were identified as significant or near-

significant factors associated with death or need for LT. However, with the use of multivariable logistic regression to adjust for confounding factors, none of these risk factors were found to be independently significant in predicting death or the need for LT. A further sub-analysis comparing the outcome of PALF between two time periods, Era 1 (2007–2013) and Era 2 (2014–2019), showed a significantly reduced mortality rate and improved spontaneous recovery rate in the latter era (Table IV).

Table III. Univariate analysis comparing factors between patients who spontaneously recovered (survived without LT) and those who died or required LT.

Risk factor	No (%) / median (range)		p-value
	Death/LT (n = 21)	**Spontaneous recovery (n = 13)**	
Clinical			
Median age (mth)	10	10	0.9576
Age < 1 yr	11 (52.4)	7 (53.8)	0.9347
Aetiology			0.1163
Metabolic	7 (33.3)	2 (15.4)	
Infectious	4 (19.0)	5 (38.5)	
Toxic/drug	0	2 (15.4)	
Indeterminate	10 (47.6)	4 (30.8)	
Hepatic encephalopathy	15 (71.4)	5 (38.5)	0.0615
Hypoglycaemia (≤ 2.5 mmol/L)	8 (38.1)	4 (30.8)	0.6687
Invasive ventilation	13 (61.9)	3 (23.1)	0.0299
Inotropic support	10 (47.6)	3 (23.1)	0.1586
Renal dialysis	5 (23.8)	2 (15.4)	0.5608
Biochemical			
Bilirubin (μmol/L)	234 (32–847)	225 (11–381)	0.1724
Direct bilirubin (μmol/L)	140 (6–529)	89 (8–249)	0.1838
Albumin (g/L)	20 (11–28)	21 (16–26)	0.7760
ALT (U/L)	1,296 (59–11,702)	1,480 (32–8866)	0.7364
AST (U/L)	2,636 (121–18,304)	3,737 (79–13,754)	0.6324
PT (seconds)	40.4 (20.0–114.7)	34.7 (20.3–72.8)	0.4252
INR	4.93 (2.00–17.13)	3.58 (1.80–9.58)	0.0993
Ammonia (μmol/L)	124 (34–2,118)	97 (29–355)	0.1414
Lactate (mmol/L)	6.5 (1.3–23.5)	3.3 (2.7–4.7)	0.0402
Creatinine (μmol/L)	49 (28–198)	42 (26–220)	0.3296

ALT: alanine transaminase; AST: aspartate transaminase; INR: international normalised ratio; LT: liver transplantation; PT: prothrombin time

Table IV. Comparison of aetiology and outcome of paediatric acute liver failure between Era 1 (2007–2013) and Era 2 (2014–2019).

Parameter	No. (%)		p-value
	Era 1 (n = 14)	Era 2 (n = 20)	
Aetiology			0.548
Metabolic	4 (28.6)	5 (25.0)	
Infectious	3 (21.4)	6 (30.0)	
Toxic/drug	0 (0)	2 (10.0)	
Indeterminate	7 (50.0)	7 (35.0)	
Outcome			0.006
Spontaneous recovery	1 (7.1)	12 (60.0)	
Death	10 (71.4)	5 (25.0)	
Liver transplantation	3 (21.4)	3 (15.0)	

DISCUSSION

To the best of our knowledge, this study is the first to review the aetiology and outcome of PALF in Singapore. The findings showed that indeterminate aetiology (seronegative hepatitis or non-A–E hepatitis) was the most common reason for PALF in Singapore. Published literature shows that the aetiologic spectrum of PALF in Singapore mirrors that of developed nations in the West.

The PALF Study Group, which comprised centres from North America and the United Kingdom (UK), published their findings of 348 children with PALF and found that the majority (49%) had indeterminate aetiology and only three patients had acute HAV infection.[13] No patient had HBV infection as a cause of PALF in their cohort. In other single-centre reports from the UK and Europe, no specific cause could be identified in the majority (37–45%) of children with PALF, while HAV and HBV infections accounted for only 5%–11% of PALF cases.[3,18,19]

Within Asia, the causes of PALF vary widely depending on geographic location. HAV is the most common cause of PALF in India, accounting for 36%–54% of cases,[2,20,21] reflecting the high baseline prevalence of HAV infection in the country. Similarly, a study from the Philippines found HAV to be the most common aetiological agent in PALF.[22] In Japan, a nationwide survey covering both adult and paediatric patients showed that viral infections accounted for about 45% of cases of acute liver failure, and the majority of these infections were HBV.[23] The same survey also found that indeterminate cause accounted for only about 28% of ALF cases in Japan.[23] By contrast, a paediatric study from Taiwan reported indeterminate cause in 14 out of 23 (61%) patients with PALF, and only four cases with infectious aetiology, comprising two patients with HBV, one patient with cytomegalovirus and one patient with Coxsackie virus.[7] Zhao et al retrospectively analysed 32 patients with PALF admitted in five hospitals in China and found that indeterminate aetiology, rather than viral hepatitis, accounted for the majority (47%) of cases.[6] Improved sanitation and food and water hygiene standards may explain the rarity of HAV-related PALF in developed Asian countries such as Singapore. The adoption of universal newborn HBV vaccination may also be an important contributing factor to the zero incidence of HBV-related PALF in our cohort. Across all studies from various parts of the world, autoimmune liver disease and toxic or drug-induced liver injury were relatively uncommon causes of PALF.

On analysing the subgroup of younger children within 12 months of age, metabolic disorders were the most common cause of PALF in our cohort, comprising a spectrum of organic acidaemia, urea cycle defect and mitochondrial disorder. While IEM are considered a group of rare diseases overall, they tend to be detected at high prevalence in young infants with PALF. In the study by Sundaram et al that examined 148 patients aged 90 days or less from the PALF Study Group registry, 38% were of indeterminate cause, while metabolic diseases (18.9%), mostly

galactosaemia, NH (13.5%) and HSV infection (12.8%) accounted for a significant proportion of cases with identified causes.[4] Similarly, reports from centres in UK and France have also established that metabolic disorders and NH were the most common aetiologies for PALF in infants, particularly in the neonatal period.[18,24,25] Recent evidence has led to the understanding that NH is the phenotypic expression of underlying GALD, a maternal-fetal alloimmune disease mediated by transplacental maternal IgG directed against fetal hepatocytes.[17] It is interesting that GALD has not been found to be a cause of PALF in our study, and it also appears to be relatively under-represented in other Asian PALF studies. We postulate that this might be attributable to differences in genetic susceptibilities between populations. Another reason could be that the difficulty and challenge in performing oral/buccal mucosa biopsy or conducting magnetic resonance imaging in a critically ill neonate with significant coagulopathy might have resulted in delayed or missed diagnosis, particularly in centres with less expertise or resources. Nonetheless, it is recommended that in the evaluation of young infants with PALF, investigations should be prioritised for early diagnosis of IEM and GALD as well as HSV infection, as some of these conditions are potentially treatable.[4]

Outcome data from our study shows that over one-third of patients survived without LT. This is similar to data from Birmingham, UK, where the reported rate of spontaneous recovery with supportive management was 33%.[18] Spontaneous recovery rate and need for liver transplantation may vary depending on the aetiology. Paracetamol toxicity (50%–94%) is associated with the highest spontaneous recovery rate, whereas indeterminate cause is associated with a comparatively lower rate of survival without LT (22%–43%).[13,18] The rate of survival without LT for metabolic disorders in these studies ranged from 27% to 44%. In our series, the lowest rate of spontaneous recovery was observed in PALF caused by metabolic disorders, which

tended to present in the younger age group. Some of these conditions encountered, such as mitochondrial disease, resulted in significant multisystem involvement, making these patients unsuitable for LT and with no other specific treatment available.

Many groups have proposed a variety of prognostic indicators to predict poor outcomes in PALF. The PALF Study Group found that peak total bilirubin ≥ 5 mg/dL, INR ≥ 2.55 and HE were independent risk factors predicting death or LT at three weeks.[13] Not surprisingly, patients with severe HE (Grade III or IV) at onset or those demonstrating HE progression were associated with the highest mortality rate.[14] Liu et al found that peak PT/INR, bilirubin and ammonia levels correlated with the risk of death in children with PALF, and devised the liver injury unit score to stratify the risk of mortality based on these parameters.[26] Lee et al found that significant independent predictors for failure of conservative therapy were time to onset of HE > 7 days, PT > 55 seconds and ALT ≤ 2384 U/L.[18] Alam et al similarly reported a jaundice-to-HE interval of ≥ 7 days and higher paediatric/model for end-stage liver disease scores at 72 hours to be associated with poor outcome.[2] Kathemann et al reported that high serum ammonia, low albumin and low ALT levels on admission were associated with worse outcome, whereas Poddar et al found that young age, HE, higher serum bilirubin and PT, and lower serum albumin were significantly associated with mortality.[19,21] In our study, serum lactate, INR, HE and need for mechanical ventilation were factors associated with death or need for LT; however, owing to the small sample size, none of these risk factors were independently significant when multivariable regression analysis was performed. The varying results derived from different groups can be explained by a few reasons. Firstly, the overall prognosis of PALF is influenced by the underlying aetiology; hence, prognostic markers may differ depending on the prevalence of specific aetiologies in distinct populations.[27] Secondly, and importantly, survival statistics and transplant rates in each

country or region are also likely to be affected by access to mature, well-established LT programmes and availability of donor organs. Therefore, results from individual centres may not be generalisable to other populations of patients with PALF.

In patients who do not recover spontaneously with supportive management, LT is the only treatment option available; however, outcomes of emergency transplantation are consistently poorer than those of elective transplantation with increased risk of sepsis, multiorgan failure and early post-transplant mortality.[1] Nonetheless, LT outcomes for ALF have steadily improved, with one-year survival exceeding 80%. In regions where shortage of size-matched deceased-donor organs remains a considerable challenge, particularly in Asian countries such as Singapore, LDLT is an important and viable option.[11,12,28,29] It has been shown that in experienced centres, LDLT for patients with PALF was associated with shorter waiting times and superior graft outcomes as compared to deceased donor LT.[9] In our study, we have reported the outcomes of six patients who underwent LDLT for PALF, and while the total LT number was small, the one-year survival rate was over 80%.

Our data also revealed the missed opportunity for LT in at least three patients who were referred for LT assessment but died before LT could be performed. Potentially, some of the patients who were considered unsuitable candidates for LT might also have missed the window of opportunity to be assessed for LT prior to the onset of multisystem complications. In our local setting in Singapore, the majority of children with PALF would present to our centre (KK Women's and Children's Hospital) for initial management. Patients who eventually failed supportive management would then be referred and transferred to the paediatric LT unit at National University Hospital. One might postulate that the delay in assessment for LT, which would be intrinsic in such an arrangement, might have contributed to fewer (17.6%) patients being offered

timely LT. Comparatively, LT rates for PALF in established liver centres are in the range of 32%–41%.[13,18] Interestingly, improved survival and spontaneous recovery rates were observed in the latter era of our cohort, although aetiologies were not significantly different between the earlier and later groups. This can be best explained by improvement in supportive care provided by the hepatology and critical care teams at our centre over time, even as transplant rates did not increase over time in the latter era.

As the data was derived from the largest tertiary paediatric hospital in Singapore, our findings could be considered to be representative of cases of PALF in the country. However, we acknowledge that this is a retrospective, observational study of an uncommon paediatric condition, with inherent limitations of ascertainment and verification bias, as well as small sample size, which could have affected the quality of statistical analysis. Nonetheless, this is the first study on PALF in Singapore, and the findings from this paper will provide useful insights and understanding of the aetiologic spectrum, prognosis and survival outcome in our local population.

In conclusion, the majority of cases of PALF in children aged above one year in Singapore were of indeterminate aetiology, while metabolic disorders were most commonly encountered in infants below one year of age. PALF is universally associated with poor survival rates, and is best managed at a dedicated LT unit to ensure seamless and timely transition from supportive management to transplant assessment for patients who will eventually benefit from LT.

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