Developmental and functional outcomes in children with chronic liver disease undergoing liver transplant: a longitudinal cohort study

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A Dissertation submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Science in Physiotherapy.

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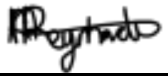
Declaration

I, Kyara Megan Reynhardt, declare that this Dissertation is my own, unaided work. It is being submitted for the Master of Science, Physiotherapy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

_Kyara Reynhardt_____ 

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Abstract

Background: Chronic liver disease has multiple negative implications and has been shown to result in impairments in neurodevelopment and health-related quality of life. Minimal research has been conducted in a South African context on the effects of liver disease on neurodevelopment and health-related quality of life in children undergoing liver transplantation.

Objectives: To determine neurodevelopment and health-related quality of life both pre- and post- liver transplantation in children with chronic liver disease under the age of five years undergoing liver transplant and to evaluate change over time.

Methods: Neurodevelopmental assessment using the Ages and Stages Questionnaire and health-related quality of life assessment using the Paediatric Quality of Life Inventory Scale were conducted pre-liver transplant and at three month post-liver transplant in ten children with chronic liver disease under the age of five years. Functional status was determined using the Functional Status Score and evaluated pre-operatively, immediately post-operatively, at ICU and hospital discharge and at a three month follow up. Comparisons and change over time were determined for each participant.

Results: Ten children, with chronic liver disease, under the age of five years undergoing liver transplant were assessed. Of that, three were at risk for delay in communication, five showed delays in gross motor skills, four showed delays in fine motor skills, four showed delays in problem solving skills and one showed delay in personal social skills on pre-operative assessment. Post operatively, two showed delays in communication skills, four showed delays in gross motor skills, three showed delays in fine motor skills, two showed delays in problem solving skills and two showed delays in personal social skills. Lower scores were shown in health-related quality of life physical health scores pre-operatively. Post-operatively three children had a reduced total score on Paediatric Quality of Life Inventory Scale compared to pre-operative scores and four showed improvement in overall health-related quality of life post-transplant.

Conclusion: Chronic liver disease can result in impairments in neurodevelopment and health-related quality of life in children under five years of age. Despite liver transplantation, some children still presented with delay in neurodevelopment post-operatively and showed a reduction in health-related quality of life at three months post-transplant. Improvement in health-related quality of life was seen in the majority of participants post-liver transplant.

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List of Abbreviations

- ABAS-II Adaptive Behaviour System-II Scale
- ADL Activities of Daily Living
- ALF Acute liver failure
- ALGS Alagille's Syndrome
- ASQ-3 Ages and Stages Questionnaires, Third Edition
- A1ATD Alpha-1 antitrypsin deficiency
- BA Biliary Atresia
- CLD Chronic Liver Disease
- CPCCRN Collaborative Paediatric Critical Care Research Network
- ESLD End Stage Liver Disease
- FSS Functional Status Score
- HE Hepatic Encephalopathy
- HPS Hepatopulmonary Syndrome\
- HRS Hepatorenal Syndrome
- HRQOL Health-related Quality of Life
- ICU-AW ICU-acquired weakness
- KPE Kasai Portoenterostomy
- LT Liver Transplant
- LDLT Living Donor Liver Transplantation
- LoS Length of Stay
- MDT Multidisciplinary Team
- MUAC Mid Upper Arm Circumference
- PedsQL Paediatric Quality of Life Inventory Scale
- PELD Paediatric End-Stage Liver Disease score
- PFIC Progressive Familial Intrahepatic Cholestasis
- PHT Portal Hypertension
- PCPC Paediatric Cerebral Performance Category
- PMSA Psoas Muscle Surface Area!
- POPC Paediatric Overall Performance Category
- PROM Patient Reported Outcome Measures
- PSC Primary Sclerosing Cholangitis

- PTLD Post-transplant Lymphoproliferative Disorder
- QoL Quality of Life
- RLD Related living donor
- WDGMC Wits Donald Gordon Medical Centre

Chapter 1 Introduction

1.1 Background

Knowledge of normal childhood development and the interactions between developmental, behavioural, social, and environmental factors plays an important role in understanding and advocating for child health (Hsieh et al., 2013). We see developmental delays in the paediatric populations of both upper and low-middle income nations. Neurodevelopmental delay may limit a child's ability to perform daily functional activities and negatively impact their ability to participate in their environment at an age-appropriate level (Rodijk et al., 2020). There are various factors that can negatively impact a child's neurodevelopment, such as chronic illness and frequent hospitalisation. Children with chronic illness often report lower health-related quality of life when compared to the healthy population (Konidis et al., 2015; Mohammad et al., 2016).

Hepatic and hepatobiliary diseases, often resulting in end-stage liver disease (ESLD), are a common cause of morbidity and mortality in children (Dhole et al., 2015). Chronic Liver Disease (CLD) is defined as long-standing, irreversible change in the hepatic structure that may result in complications, such as cirrhosis, leading to a premature death (Dhole et al., 2015) Liver transplantation has proven to be successful in treating children with ESLD and is leading to prolonged life expectancy in this patient cohort (Almaas et al., 2015). The main indications for liver transplant in children include extra-hepatic cholestasis, such as Biliary Atresia; intra-hepatic cholestasis, such as Alagille's Syndrome; metabolic diseases, such as Wilson's disease and α1-antitripsin deficiency; Acute Liver Failure and malignancies of the liver (Marcdante et al., 2023). Of these, Biliary Atresia (BA) is the most common cause of CLD and liver transplantation in the paediatric population (van der Schyff et al., 2021).

Biliary atresia is defined as a progressive fibrosing cholangiopathy, with onset most often in the first three months of life. The worldwide incidence of BA is one in 20,000 live births with a five-year survival rate of approximately 42- 59% in developed countries. The percentage of patients with BA that will ultimately require liver transplant

ranges between 53-78%, internationally (van Heerden et al., 2019). In the South African context, cholestatic liver disease, predominantly BA, is the cause for over half the paediatric liver transplants performed at the Wits Donald Gordon Medical Centre (WDGMC) between 2014 and 2018. Of this, most of the paediatric transplant recipients were female (61.6%) and under five years of age (73.6%) (Fabian et al., 2019). The most common indications for transplant include failed Kasai, failure to thrive, cholangitis, portal hypertension, hepatopulmonary syndrome and hepatorenal syndrome (Sundaram et al., 2017).

Children with chronic liver diseases are prone to various complications, from poor nutrition and growth deficits to recurrent and prolonged hospital admissions. Some of the complications of liver failure, including sarcopenia, hepatic encephalopathy, and failure to thrive, can impact the functional ability and quality of life of affected children (Santos et al., 2021). Due to chronic malnutrition and vitamin deficiencies growth failure is common in this patient population. Sarcopenia and pathological fractures, due to osteopenia, may be present in some patients, especially as liver disease progresses (Högler et al., 2010; Sundaram et al., 2017a). This can further impact the growth and development of children with CLD. As a result, developmental delays may often be present.

Due to the nature of liver disease, these children are exposed to a variety of risk factors including recurrent hospital admissions, infections and reduced motor activity which can affect both cognitive and motor developments (Almaas et al., 2015). Studies have shown that children with Biliary Atresia have impaired neurodevelopment compared to age-matched healthy children, with motor outcomes being the most affected (Rodijk et al., 2020). In BA, pre-transplant nutritional, weight and height deficits are associated with poor patient and graft survival post-transplant, therefore optimisation of these patients prior to surgery is crucial (Takeda et al., 2021). Research emphasises the importance of nutritional optimisation, with few studies mentioning physical or functional optimisation pre-operatively.

Sarcopenia is defined as the progressive loss of skeletal muscle mass and strength and results in a decline in physical function, with persistent sarcopenia being associated with poor development in children. It is a frequent complication in patients with liver cirrhosis due to impaired protein synthesis (Takeda et al., 2021). In a recent

study, sarcopenia was associated with a longer ventilator duration and an increased length of stay in hospital in children post-liver transplant (Takeda et al., 2021). The presence of sarcopenia negatively impacts core muscle strength, which is important for head control, rolling, sitting, and standing, and ultimately affects the motor development of the child. The presence of associated complications, such as ascites and peripheral oedema may also impact the functional ability of a child with CLD (Takeda et al., 2021). From this, we can see that the liver failure can negatively impact the growth, development of children with CLD.

Furthermore, it is also important to consider the impacts on neurodevelopment and quality of life both pre- and post-liver transplant. In a study completed by Kamath et al. in 2015, the health-related quality of life (HRQOL) in children with liver disease was found to be significantly lower when compared to healthy. The largest effect seen was in the physical domain of the questionnaire (Kamath et al., 2015, 2018). This highlights the deficit in physical development that may often be present in CLD. With the average 10-year survival rate post-transplant being >80%, the importance of medical, psychosocial, and physical complications and the effect on quality of life has been emphasised (Konidis et al., 2015). It is reported that the overall HRQOL improves post-transplant, however, paediatric recipients have self-reported HRQOL scores that are lower compared to the healthy population but are comparable to those with chronic illnesses (Konidis et al., 2015). When looking at this cohort of patients, it is therefore important to consider how the condition and the various complications may impact their function and ultimately, quality of life.

1.2 Problem Statement

Limited access to adequate health-care facilities, often resulting in delayed referral, may impact the outcome of this patient population. Malnutrition is prevalent in more than half the patients that were transplanted for BA between 2005 and 2017 at WDGMC (van Heerden et al., 2019). Studies conducted by the research team and physicians at WDGMC have highlighted the presence of malnutrition and emphasised the need for nutritional optimization in order to improve post-operative outcomes. However, there has been minimal research, specifically within the South African context, regarding physical, developmental, and functional outcomes and the effects on quality of life for these children.

1.3 Aims and Objectives

Aim:

To investigate the developmental and functional outcomes and the effects on quality of life in children with chronic liver failure undergoing transplant.

Objectives:

- To determine the developmental status of children with chronic liver disease awaiting transplant, younger than five years of age, using the Ag es and Stages Questionnaire (ASQ-3).
- To assess health-related quality of life in children awaiting liver transplant using the Paediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scale and Infant Scales.
- To determine the functional status of children in ICU post-liver transplant using the paediatric FSS.
- To determine the developmental status of children with chronic liver disease 3 months post- transplant, younger than five years of age, using the ASQ-3.
- To assess health-related quality of life in children post liver transplant using the PedsQL at three months post-transplant.
- To describe any functional impairments that may be present in children with chronic liver disease awaiting transplant, post-transplant and at three-months post-transplant.
- To describe the HRQOL of children with chronic liver disease awaiting liver transplant
- To describe the HRQOL of children with chronic liver disease post-liver transplant at a three-month follow-up

1.4 Significance

Wits Donald Gordon Medical Centre is the primary centre for paediatric liver transplantation in South Africa for both private and state patients and is currently the only facility that offers living-donor transplants in Sub-Saharan Africa.

The results of this study will be significant in terms of advocating for early referral of patients with CLD, not only for nutritional optimisation, but for developmental and physical rehabilitation as required in order to improve the long-term outcomes of children undergoing liver transplant.

1.5 Outline of Dissertation

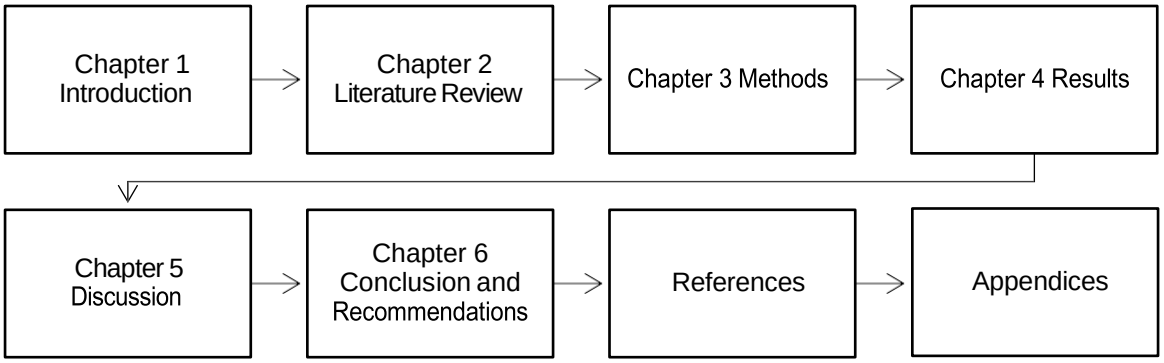

Figure 1-1. Outline of the thesis

Chapter 2 Literature Review

2.1 Introduction

The following review will discuss the epidemiology, aetiology and pathology related to paediatric chronic liver disease. Complications of chronic liver disease and the potential effects this has on development and quality of life will be included.

Information on the causes, criteria, and outcomes of liver transplantation, worldwide and in South Africa, will be discussed in this review article.

Childhood development and the effect of chronic illness of development will briefly be discussed to provide insight on effects on health-related quality of life. Three standardised paediatric outcome measures, the Paediatric Quality of Life Inventory Scales; The Functional Status Score and the Ages and Stages Questionnaire, will be outlined.

2.2 Search Strategy

Key words: Biliary Atresia; Liver transplant; Paediatric Liver Failure; Sarcopenia; Neurodevelopmental milestones; Chronic Liver Failure; Chronic paediatric illness; Quality of Life; PedsQL; ASQ3; FSS; Alagille's Syndrome; Malnutrition; PFIC; Liver transplant, Paediatric liver transplant

Search Engines: PubMed, Clinical Key, Google Scholar, Springer Link, WHSL, Elsevier

English language articles were sourced and used. Articles included were published in English from 2010 onwards.

2.3 Paediatric Liver Disease

2.3.1 Acute Liver Failure

Acute liver failure (ALF) is a rare occurrence but progresses quickly into a life-threatening condition with severe hepatic dysfunction. The main causes of ALF in infants may be of viral origin, such as enterovirus infection, inherited metabolic diseases or hemochromatosis. In older children, causes are often drug-induced or as a result of toxins, autoimmune hepatitis, and viral infections such as Hepatitis A

(Cuenca et al., 2017; Dias Costa et al., 2018). Patients with ALF may spontaneously recover hepatic function. The decision to transplant is typically made at a point where there is no clinically significant recovery in liver function. Factors including encephalopathy related to hyperammonemia, raised intercranial pressure and cerebral oedema indicate the need for urgent transplantation (Cuenca et al., 2017).

2.3.2 Chronic Liver Disease

Chronic Liver Disease (CLD) is defined as progressive deterioration of liver functioning for a period greater than six months involving continuous inflammation, destruction and regeneration of the liver leading to fibrosis and cirrhosis, the final stage of CLD (Sharma & Nagalli, 2022). There are various causes resulting in CLD, ranging from congenital or metabolic disorders to autoimmune and viral diseases (Ozdogan & Arikan, 2023).

Liver fibrosis and cirrhosis presents a major health burden worldwide, regardless of age, sex, ethnicity, or region with a global prevalence of cirrhosis, as a result of acute or chronic liver failure, being between 4.5%-9.5% of the general population (Ali et al., 2020). The prevalence of CLD has increased with new diagnostic strategies and is a common cause of mortality especially in developing countries (Sharma & Nagalli, 2022). There is limited information on the prevalence related to paediatric CLD in the general population. However, there is some data available on the prevalence of specific conditions related to chronic end-stage liver disease which will be discussed further. Cholestatic Liver Disease, which involves any condition in which there is reduced bile flow, occurs in approximately 1:2500 new-borns in North America (Karpen, 2020).

In Africa, liver cirrhosis in the general population results in approximately 53,000 to 103,000 deaths per year (Ali et al., 2020). In South Africa, there is limited information on the epidemiology of paediatric CLD due to lack of national database. However, the Transplant Unit at Wits Donald Gordon Medical Centre (WDGMC) produces annual reports on paediatric liver transplants which provides some insight into the incidence of paediatric liver disease and liver transplantation which will be discussed in further detail.

2.3.3 Causes and management of Chronic Liver Disease

There are a variety of conditions that result in chronic and end-stage liver disease in the paediatric setting. Biliary Atresia is the most common cause for liver failure in infants followed by inherited metabolic disorders, genetic and biliary abnormalities. Common causes of CLD in older children include auto immune and chronic viral hepatitis, non-alcoholic fatty liver disease and inherited metabolic diseases (Nel & Terblanche, 2015).

Biliary Atresia

Biliary Atresia (BA) accounts for approximately 25%-40% of paediatric cholestatic conditions (Tessitore et al., 2021). It is defined as a progressive, fibro-obliterative disorder of the intra-and extra-hepatic bile ducts (Sundaram et al., 2017b). The worldwide incidence of BA is approximately 1 in 5-20 000 live births with onset typically occurring within the first three months of life (van Heerden et al., 2019). There are recognized subtypes of BA however the pathogenesis and prevalence of each subtype is uncertain (Sundaram et al., 2017b). Subtypes include isolated BA, syndromic BA (with associated splenic malformation or BASM) and cystic BA (CBA) each with differing prognostic implications. BASM is associated with poorer prognosis compared to CBA. Isolated BA makes up 80% of overall incidence. It is thought to occur late in gestation or as a post-natal development. BA can also be morphologically classified according to the degree of obliteration of the biliary tree. Type I: obliteration at the common bile duct accounting for 5% of cases; Type II: obliteration at the common hepatic duct and accounts for 3% and Type III: at level of porta hepatis accounting for >90% of cases (Sundaram et al., 2017b; Y. van Heerden et al., 2019). Initial symptoms include jaundice and acholic stools within the first weeks of life which progresses to fibrosis, cirrhosis, and ultimately end-stage liver failure. Fibrosis progresses rapidly in BA resulting in cirrhosis within a few weeks of birth if left untreated (Ozdogan & Arikan, 2023). Timely diagnosis is complicated by several clinical manifestations mimicking BA. Confirmation of the conditions requires liver biopsy, intraoperative cholangiography, and bile duct histology (van der Schyff et al., 2021). Treatment for BA involves surgical management via a Kasai portoenterostomy (KPE) and ultimately, liver transplantation. KPE is performed within the first 90 days of life in order to restore bile flow and delay onset of cirrhosis (Neto et al., 2015). If left untreated, survival with the native liver is estimated to be up to three years of age in 90-100% of patients, therefore early diagnosis is key in the management of these patients (Scottoni & Davenport, 2020; Y. van Heerden et al., 2019). Other treatment includes symptomatic

treatment and nutritional supplementation to optimise patients for transplant. BA is the leading cause for liver transplantation in the paediatric population. Indications for transplantation in BA include early failed KPE, failure to thrive, portal hypertension, hepatopulmonary syndrome, portopulmonary syndrome and hepatorenal syndrome (Sundaram et al., 2017a).

Alagille Syndrome

Alagille Syndrome (ALGS) is an autosomal dominant disorder affecting multiple organ systems including liver, heart, eyes, face, skeletal, kidneys and vasculature. ALGS results from mutations in two genes, JAGGED1 and NOTCH2, associated with Notch signalling pathways. Disruption in this pathway results in abnormal development of intrahepatic bile ducts (Kamath et al., 2015, 2018). Incidence of ALGS is approximately 1 in 30,000 live births (Ayoub & Kamath, 2020).Most common clinical presentations of ALGS include chronic cholestasis, congenital heart disease, butterfly vertebrae, ophthalmic abnormalities in the form of posterior embryotoxon and characteristic dysmorphic features (Kamath et al., 2018; Turnpenny & Ellard, 2012). Chronic cholestasis presents as jaundice with conjugated hyperbilirubinemia, typically during the first three months of life. The most commonly presenting cardiac symptom is peripheral pulmonary stenosis however the condition can also present with atrial and ventricular septal defects, pulmonary atresia, and Tetralogy of Fallot. Characteristic dysmorphic features are broad forehead, deep-set eyes, prominent ears, straight nose with bulbous tip and pointed chin giving the face resulting in a slightly triangular shaped face (Turnpenny & Ellard, 2012).

Chronic cholestasis occurs in approximately 95% of patients with ALGS with progressive liver disease leading to cirrhosis and fibrosis requiring liver transplantation occurring in up to 50% of patients (Ayoub & Kamath, 2020; Mouzaki et al., 2016). Many children with ALGS will present with severe pruritus from approximately six months of age which greatly diminishes quality of life. As in other cases of cholestatic liver disease, there is a deficiency in fat-soluble vitamins which can result in a variety of complications from bleeding to osteopenia and pathological fractures (Ayoub & Kamath, 2020). In the case of end stage liver disease from cholestasis, it has been noted that the presence of cardiac and vascular abnormalities may complicate the process of liver transplantation (Ayoub & Kamath, 2020). ALGS may sometimes be misdiagnosed as BA, typically during the neonatal period, which is significant as a

Kasai Portoenterostomy (KPE) may not be beneficial in ALGS (Turnpenny & Ellard, 2012).

Alpa-1 Antitrypsin Deficiency

Alpha-1 antitrypsin deficiency (A1ATD) is an inherited autosomal disorder affecting the A1AT protein. A1ATD predisposes one to liver and lung disease with the most severe presentation occurring in 1:3500 live births however, it may be misdiagnosed or underdiagnosed (Mitchell & Khan, 2017). In A1ATD there is a proteinopathy, abnormal synthesis and function of the A1AT protein, which is produced in the liver, which results in a proteotoxicity. Liver disease associated with A1ATD results from accumulation of misfolded A1AT in hepatocytes which leads to hepatic fibrosis (Mitchell & Khan, 2017). In the case of ESLD resulting from A1ATD, liver transplantation is required.

Progressive Familial Intrahepatic Cholestasis

Progressive familial intrahepatic cholestasis (PFIC) is a group of autosomal recessive genetic disorders affecting intrahepatic bile flow. A disruption in the genes encoding protein transporters that are responsible for bile formation resulting in impaired flow of bile leading to intrahepatic cholestasis and progressive liver failure. It is estimated to affect one in 50,000 – 100,000 live births with early onset presentation being common from the neonatal period through the first year of life (Alam & Lal, 2022; Mehl et al., 2016). PFIC is subdivided into PFIC1, PFIC2, PFIC3 and PFIC4 based on the specific gene mutations that occur all presenting with common features although onset and progression to ESLD can occur at different stages ranging from the neonatal period to infancy and early childhood (Mehl et al., 2016).

2.3.4 Complications associated with Chronic Liver Disease

There are multiple associated symptoms and complications that accompany CLD, some are more disease specific whilst others can be applied to the general patient population. Many of these complications may negatively impact the child's quality of life as well as the rates or morbidity and mortality.

Nutritional Deficiency

Malnutrition is present in more than half the paediatric population of chronic liver disease and approximately 60%-80% of those awaiting liver transplant (Normatov et al., 2018). It is associated with reduced quality of life and increased morbidity and

mortality rates in both pre- and post-transplant patients (Normatov et al., 2018). The degree of malnutrition is associated with severity of liver disease. The relationship between CLD and malnutrition is complex, with CLD leading to malnutrition and the presence and severity of malnutrition adversely affecting the course of liver disease (Nel & Terblanche, 2015). Nutritional deficiency in CLD is multifactorial and can present in a variety of ways. Potential causes of malnutrition include reduced nutrient intake, malabsorption or maldigestion, increased metabolic demands and endocrine dysfunction (Normatov et al., 2018; Tessitore et al., 2021). It has been noted that resting and total energy expenditure are increased by 30% (Nel & Terblanche, 2015).

A decreased nutritional intake in children with CLD can result from nausea and vomiting due to presence of organomegaly and ascites and subsequent decreased gastric capacity leading to feelings of early satiety. Anorexia is present in some children with CLD and is related to a decrease intake as well as a change in the metabolism of amino acids (Tessitore et al., 2021).

It is important to consider the function of the liver and the role it has in digestion and absorption to better understand the nutritional deficiencies present in these children. The liver functions to maintain metabolic homeostasis and assists in digestion, distribution, and storage of nutrients. Metabolic pathways are altered due to the decrease in hepatic and muscular glycogen reserves. As a result, there is an increase in the release of amino acids, increased fat oxidation and the rapid use of fat stores. Bile is produced by the liver and is secreted and stored in the gall bladder. Its main functions are to assist in the digestion of fats via emulsification and the absorption of fat-soluble vitamins, A; D; E and K (Almajid & Sugumar, 2022). The main nutritional deficiencies present in children with CLD are the fat-soluble vitamins and this can result in a variety of complications which will be discussed in further detail throughout this literature review. Clinical signs of fat-soluble vitamin deficiencies can be seen as early as four to 12 months in cases where cholestasis begins during infancy therefore supplementation is important in these infants (Tessitore et al., 2021)

Vitamin A is important for a variety of biological functions including vision, immunity, maintenance of cell functioning and growth, red cell production, reproduction, and pulmonary function (Sathe & Patel, 2010). Deficiency presents in multiple ways, most commonly with night blindness. However, in terms of the CLD patient population,

significant effects of vitamin A deficiency include anorexia, leukopenia and anaemia, reduced helper T-cell functioning and impaired mucous secretion (Sathe & Patel, 2010). It is important to note that excessive amount of vitamin A may result in further hepatic and neurological damage therefore needs to be closely monitored (Tessitore et al., 2021).

Vitamin D is crucial in bone metabolism. Deficiency most commonly presents with rickets (Sathe & Patel, 2010). Hepatic osteodystrophy is a common symptom associated with CLD and results in osteoporosis and osteopenia or rickets in the paediatric population. As a result, pathological fractures are common complications and can have a negative impact on quality of life as well as post-transplant outcomes (Nel & Terblanche, 2015).

Vitamin E is vital for immune functioning with deficiency leading to haemolytic anaemia and neurological deficits (Sathe & Patel, 2010). Deficiency in vitamin E may initially be asymptomatic but can be difficult to treat in severe cholestasis, requiring high doses of supplementation. Children may develop peripheral neuropathy, ataxia, and spinocerebellar degeneration as a result of vitamin E deficiency (Nel & Terblanche, 2015).

Vitamin K has a functional role in calcium-dependent protein activities that are involved in coagulation as well as maintaining bone homeostasis. Deficiency in Vitamin K is common in cholestatic diseases such as ALGS and BA affecting up to two thirds of this patient population. Patients with CLD can present with coagulopathies, with vitamin K deficiencies monitored by prothrombin time and internation normalised ratio (INR) and can therefore complicate with an increased risk of bleeding. (Licata et al., 2021; Nel & Terblanche, 2015) .

Sarcopenia

Sarcopenia is defined as unintentional muscle loss or wasting accompanied by loss of physical function (Lurz et al., 2018; Takeda et al., 2021). In the adult population, sarcopenia is a well researched condition but is a relatively new, under-researched concept in the paediatric population (Lurz et al., 2020). It is a common complication in patients with CLD, liver cirrhosis and end-stage liver disease who are typically awaiting liver transplant and can be an indicator of nutritional status. Sarcopenia in children

differs to that of adults as it is not related to muscle disuse but rather a complication of malnutrition, neurodevelopmental and hormonal factors (Rezende et al., 2020; Takeda et al., 2021). As mentioned previously, there is often a reduced dietary intake in these children, malabsorption of nutrients and an increased metabolic demand which can all contribute to the presence and severity of sarcopenia in children with CLD. In addition, liver glycogen stores are depleted due to the fibrosis and cirrhosis of the liver which leads to protein catabolism for gluconeogenesis and energy metabolism to take place thus reducing muscle mass. Muscle mass is further impacted by impaired protein synthesis due to reduced availability of amino acids and chronic hyperammonaemia. This all leads to a progressive deterioration and loss of muscle mass (Merli, 2020). In some cases, there can be increase in adipose tissue due to physiological compensation for the loss of lean muscle mass. This results in sarcopenic obesity, which is the presence of increased weight in the presence of sarcopenia (Rezende et al., 2020). In addition to the physiological factors that are associated with sarcopenia in CLD, it is important to consider the impact of reduced physical activity that accompanies chronic illness (Rezende et al., 2020). It is noted that loss of lean muscle mass is an indicator of poor prognosis in both pre-transplant and post-transplant (Rezende et al., 2020). Post-transplant morbidity and length of stay in hospital is also associated with the presence, and severity, of pre-transplant sarcopenia (Lurz et al., 2018).

A predictor of sarcopenia is the loss of total psoas muscle surface area (Lurz et al., 2018). In a study completed by Lurz et al., comparing psoas muscle surface area (PMSA) at L3/L4 and L4/L5 level measured using CT imaging, patients with ESLD were compared with healthy controls. Results of the study showed that children with ESLD had significantly smaller total psoas muscle surface area than matched healthy controls (Lurz et al., 2018). The gold standard method for determining sarcopenia is by measuring the psoas muscle surface area via CT imaging, however this is not universally accessible therefore anthropometric measurements are relied on in majority of cases. Outcome measures such as mid upper arm circumference (MUAC), weight and height measurements are used (Lurz et al., 2018; Rezende et al., 2020). However, due to the presence of conditions associated with CLD such as sarcopenic obesity, peripheral oedema, ascites and organomegaly, anthropometric measurement may not be a true indicator of nutritional deficiency and the presence of sarcopenia (Lurz et al., 2018; Rezende et al., 2020).

Measuring muscle function is an important component of assessing sarcopenia as the loss of muscle strength and function is associated with muscle loss and wasting. However, there is a lack standardised measurements for muscle strength and function in infants and young children compared to adults (Merli, 2020). Therefore, functional developmental assessments can be used in ascertaining muscle strength. This includes observing stability, co-ordination and presence and effectiveness in purposeful movements in infants and young children (Merli, 2020).

Osteopenia

Bone length and strength are often affected with ESLD leading to hepatic osteodystrophy and growth failure. Hepatic osteodystrophy associated with malnutrition and physiological changes can be a common complication in CLD and ESLD (Högler et al., 2010). Causes of hepatic osteodystrophy are multifactorial and are associated with malnutrition and malabsorption, impaired protein synthesis, reduced mobility, or physical activity as well as potential hypogonadism with vitamin D deficiency being one of the major contributing factors. Hepatic osteodystrophy in children affects both existing bone as well as growth plates which can lead to rickets, spinal abnormalities and low bone mass and can ultimately lead to growth failure (Högler et al., 2010; Nel & Terblanche, 2015). There is a link between the presence of sarcopenia and low bone mass, with sarcopenia being a common complication of liver disease (Högler et al., 2010). A lower BMI, associated with sarcopenia, is associated with an increased risk of osteopenia (Jeong & Kim, 2019).

It is important to consider that bone density is not resolved immediately after liver transplantation. Studies have shown that there is a greater incidence of fracture immediately after LT, with an estimated 12% to 38% prevalence post-transplant (Högler et al., 2010; Jeong & Kim, 2019). The prevalence of pre-transplant osteodystrophy is linked to the risk of post-transplant bone mass deficiencies and fractures. Vitamin D levels may remain low immediately after transplant, thus affecting the risk of bone fractures, however these levels do improve during the first year post-LT. Another factor affecting bone health immediately post-transplant is the use of immunosuppressants, specifically glucocorticoids. Bone resorption is stimulated while bone formation is reduced. This is typically more prevalent during the first six to twelve months following transplantation (Jeong & Kim, 2019).

Portal Hypertension and Hepatopulmonary Syndrome

Portal hypertension (PHT), defined as increased pressure within the portal venous system, can develop following progressive hepatic fibrosis and occurs in majority of children with CLD. It is associated with significant morbidity and mortality in children and can result in gastro-and oesophageal varices which lead to upper gastrointestinal bleeding (Sundaram et al., 2017c).

Hepatopulmonary Syndrome (HPS) is characterized by arterial hypoxemia as a result of intrapulmonary vascular dilations present in patients with PHT. Patients commonly present with signs of hypoxia and fatigue. HPS occurs in 3%-20% of children with cirrhosis. PHT and HPS are both have high mortality rates without transplant but are both reversible following LT (Sundaram et al., 2017b).

Hepatorenal Syndrome

Hepatorenal Syndrome (HRS) is a rare complication associated with ESLD and involves acute renal failure that is secondary to reduced renal blood flow. HRS typically resolves following LT (Sundaram et al., 2017c).

Pruritus

Pruritus or itching is a symptom associated with CLD and cholestasis. It is as a result of the accumulation of bile acids due to defective bile drainage (Tessitore et al., 2021). It is most commonly reported in patients with ALGS and PFIC but can also be present in patients with BA. It can be significant enough to impair quality of life for the child and their family (Sundaram et al., 2017c).

2.3.5 Chronic Liver Disease and Quality of life

Chronic liver disease, as with many other chronic illnesses, is often associated with severe complications and co-morbidities resulting in frequent hospitalisations and increased mortality. Many of the complications that arise from CLD may have debilitating consequences for patients which can impact their ability to perform age-related ADLs and their overall quality of life (QoL) (Grønkjær & Lauridsen, 2021). QoL is defined as an individual's perception of their position in life according to their culture and social values (Demiral et al., 2021). Linked to this, especially within the context of chronic illness, is the concept of health-related quality of life (HRQOL). HRQOL is

provides a comprehensive evaluation of the impact of an illness and the related treatment on a patient's function and wellbeing (Parmar et al., 2017).

Kamath et al., 2015 performed a cross-sectional study observing HRQOL using the PedsQL in patients with genetic causes for intrahepatic cholestasis (IHC) such as ALGS and A1ATD. The study included a total of 98 subjects with ALGS, 95 with A1ATD and 49 with IHC. When compared with healthy population data, ALGS, A1ATD and IHC all reported lower scores in HRQOL. The ALGS population demonstrated significant impairments, specifically within the physical domain compared to the healthy population. Features of ALGS, such as severe pruritus and growth failure, appeared to be a major determinant of reduced HRQOL. When comparing results of the PedsQL across ALGS, A1ATD and ICH, ALGS showed consistently worse scores in parent proxy reports. Patient self-reports on HRQOL showed similar results across all domains for AGLS and IHC with both scoring more poorly than those with A1ATD (Kamath et al., 2015). A cross sectional study by Mohammad et al,. 2016 observing HRQOL in infants with CLD compared to healthy controls using the PedsQL Infant Scales. The study found that in the 1-12 months age-group scores by parent report were significantly lower across all domains compared to healthy controls. In the 13-24 month age group, scores were lower in the Physical Health Summary Score and Physical Functional scores (Mohammad et al., 2016).

2.4 Paediatric Liver Transplantation

Liver transplantation is the often the main, or only, treatment option for patients with ESLD with an estimated incidence of over 30 000 children worldwide receiving transplant over the last four decades. Paediatric liver transplant accounts for approximately 7%-8% of liver transplants with around 600 children being transplanted per year in the United States (Baumann et al., 2022; Pham & Miloh, 2018).

Liver transplantation is indicated when the risk of mortality from liver failure is greater than the risk of transplantation (Cuenca et al., 2017). According to the European Liver Transplant Registry (ELTR) which covers more than 31 countries across Europe, the main indications for paediatric liver transplant are congenital biliary disease such as BA and ALGS (44%), metabolic diseases (18%), ALF (acute liver failure) or subacute liver failure (12%) with BA accounting for 39% of transplants. (Baumann et al., 2022).

The transplanted organ may be of cadaveric origin, which can be a split or whole liver or from a living donor. Living donor (related or non-related) liver transplantation (LDLT) has increased the availability of organs and allowed for decreased waitlist mortality in suitable candidates. Living donor transplantation accounted for 5% of all LT and 12% of paediatric LT in the United States in 2015 (Cuenca et al., 2017). Eligibility of patients to be waitlisted to undergo transplant involves a multidisciplinary approach and is largely determined by the Paediatric End-Stage Liver Disease (PELD) score (Pham & Miloh, 2018). The PELD score is the current way of prioritising children between the ages of 0-11 years on the waitlist for liver transplantation according to severity of illness and the risk of 90-day mortality (Chang et al., 2018). The goal of the PELD is to minimise the prevalence of waitlist mortality by using objective, quantitative measures to predict short-term mortality (Swenson et al., 2019). Measures include biological measures of liver function including international normalised ratio (INR), albumin and bilirubin levels (Chang et al., 2018). However, many patients may be listed despite low PELD scores due to the presence of co-morbidities associated with ESLD that may complicate survival such as PHT, refractory pruritus, pathological fractures, intractable ascites, and failure to thrive (Pham & Miloh, 2018).

Survival rates of LT have improved significantly and continue to improve with advancing surgical and medical management from pre-operative to post-operative period with most transplant centres reporting a one-year patient survival rate of >90% and a five-year survival rate of >80% (Cuenca et al., 2017). Although outcomes of LT have improved over recent decades, the prevalence of pre-LT co-morbidities as well as post-transplant complications such as infection, rejection, and post-transplant lymphoproliferative disorders (PTLD) impact long-term survival rates (Cuenca et al., 2017; Kitajima et al., 2017; Sundaram et al., 2017c).

Liver transplantation in South Africa

There is currently no national database for annual liver transplant statistic, therefore we are only able to receive statistics from individual transplant centres. WDGMC is home to the largest adult and paediatric liver transplant programme in South Africa. The programme was initiated in 2004 and services patients from both the State and Private Sectors (Fabian et al., n.d.). In statistics from the 2020 annual report 738 transplants for acute and chronic ESLD were performed of which 247 were paediatric transplants from the inception of the programme. The LDLT programme for paediatrics

was introduced in 2012 to help mitigate the shortage of deceased donor organs. Despite the LDLT programme, many adults and children are still lost due to ongoing organ shortages which was further impacted by the COVID-19 pandemic. (Bouter et al., 2023). A factor to consider when observing the number of deceased donor organs is the wide variety of cultural practices within South Africa's diverse population.

The 2021 annual report from WDGMC showed that in 2020 and 2021, 39 and 25 paediatric patients, respectively, were transplanted. In 2020, 67% of paediatric transplants were for children under the age of five. Of the 25 children transplanted in 2021, 20 were living donor transplants and five were from deceased donors. Reasons for transplant were as follows: ALF (20%), cholestatic disease (48%), metabolic disease (20%), malignancy (4%) and other non-specified reasons (8%). Of the patients with BA that received transplant, 73% had a previous KPE. The median number of days spent in hospital after surgery was 19 days. Unadjusted patient survival estimates for one month, one year and three year was 92% (83-96), 83% (73-90) and 66% (53-77) respectively (WDGMC Research Unit and Transplant Unit, 2022).

2.4.1 Pre-transplant Management

Management of patients' pre-transplant is crucial in order to optimise them for surgery and improve their post-operative outcomes. A multidisciplinary approach should be used in both conservative and surgical management of patient with the aim of minimising the effects of liver disease such as rickets, muscle loss and haemorrhagic disease (Nel & Terblanche, 2015). The impact of the effects of liver disease on neurodevelopment should also be considered during pre-transplant management (Santos et al., 2021).

Nutritional management is emphasised in order to optimise the patient prior to transplantation. One of the key predictors of successful liver transplants is the nutritional status at the time of surgery. Optimal management includes regular nutritional assessment throughout the pre-operative period to guide the degree of nutritional rehabilitation. It is important to account for weight gain due to organomegaly, ascites and oedema therefore relying on anthropometric measurements together with biochemical markers is more accurate than relying on weight gain alone (Sundaram et al., 2017c; Tessitore et al., 2021). Due to the malabsorption of fat-soluble vitamins and high energy expenditure of these patients, high calorie intake is encouraged and supplemented by the use of multichain triglyceride (MCT) oil which is less dependent

on bile acids for absorption. Oral feeding is often supplemented with nasogastric feeding to ensure adequate calorie intake. Additional nutritional optimisation offered in the form of total parenteral nutrition has shown to improve nutritional status without adverse clinical and biochemical effects (Tessitore et al., 2021). Increased protein intake is required in children with CLD to counteract muscle proteolysis and support catch-up growth, specifically in cases of failure to thrive (Tessitore et al., 2021).

There is limited research on physical management and strengthening prior to transplant in the paediatric population. However, it is known that physical activity and resistance exercise programmes promote muscle mass and strength in sarcopenic adults (Smith et al., 2022). Physical optimisation and nutritional optimisation of patients pre-transplantation should occur simultaneously to aid in improving patient outcomes.

Management of additional complications, such as PHT, prior to transplant may be indicated. PHT can result in ascites, hypersplenism and variceal bleeding. In the case of severe ascites that cannot be managed by medication alone, drainage via paracentesis may be indicated. The presence of severe ascites and organomegaly may lead to respiratory compromise and feeding difficulties. Variceal bleeding may require endoscopic intervention and medication to control. Thrombocytopenia and neutropenia are common complications of hypersplenism. Persistent bleeding related to the thrombocytopenia can be managed with partial splenic embolization (Sundaram et al., 2017c). Treatment of associated infections, such as bacterial cholangitis, with antibiotics may be indicated.

Surgery in the form of KPE is indicated and recommended in patients with BA within the first 90 days of life to create a pathway for bile flow. KPE may delay the need for transplantation in infants with early diagnosis of BA. The reported five-year survival rate with native liver post-KPE is 42%-59% in upper income countries.

2.4.2 Impact of Liver Transplantation on Quality of Life

With the advances in medical and surgical management, the long-term survival of patients after liver transplantation has increased with a 10-year survival rate >80%. This has resulted in an increased interest in the impact and management of long-term effects and how this may impact a child's and caregiver's wellbeing and HRQOL (Almaas et al., 2015; Konidis et al., 2015).

It is known that children with chronic illness tend to have a lower HRQOL in comparison to healthy children. This is likely due to the effects that the illness and the complications of disease can have on function. It is well established that many children with CLD present with malnutrition and growth failure associated with malabsorption and vitamin deficiency as well as many complications that could cause pain and discomfort such as abdominal distension associated with ascites and risk of pathological fractures prior to transplantation. With transplantation, absorption should improve thus improving nutritional outcome and growth. However, paediatric liver transplant recipients have a lower overall HRQOL compared to healthy children in the early post-operative period up which can last up to two decades post liver transplant (Almaas et al., 2015; Kamath et al., 2015). A systematic review conducted by Parmar et al. including 25 studies evaluating HRQOL after liver transplantation, using generic and disease-specific tools, demonstrated an overall impairment in HRQOL after LT in comparison to healthy controls but is comparable to that of children with other solid organ transplantation and chronic illness (Parmar et al., 2017). In a multicentre study conducted in the United States, HRQOL of 873 liver transplantation recipients, aged two to 18 years was compared to that of children with chronic illness using the PedsQL Generic Core Scales. The outcome of the study showed that although some differences in domains were present, the overall HRQOL in LT recipients is similar to that of children living with chronic illness (Limbers et al., 2011). This may be associated with adverse effects of medication and immunosuppression that can result in frequent hospitalisation, recurrent infections, renal dysfunction and posttransplant lymphoproliferative disorder (PTLD). Medication adherence has also been shown to impact HRQOL with nonadherent patients scoring significantly lower in all domains of PedsQL, CHQ-PF50 and CHQCF-87 (Parmar et al., 2017). The immediate post-transplant period can come with complications resulting in prolonged ICU and hospital admissions which can be a traumatic experience for the child, especially for children transplanted at older age who are better able to understand the situation. It is shown that children transplanted at older age demonstrate a lower HRQOL and that as they enter adolescence, increased awareness of their condition and the interference on day-to-day life further impacts their perceptions. It is important monitor for signs of anxiety and depression which has been reported in approximately 17.7% of LT recipients. As children reach school-going age, LT recipients might experience difficulty often related to absenteeism for medical requirements (Parmar et al., 2017).

Despite transplantation, many children still continue to experience challenges of chronic illness therefore it is important for clinicians and family members to consider the HRQOL as they grow and develop.

2.5 Childhood Neurodevelopment

Infancy and early childhood are periods over which growth and development of skills such as cognitive, motor, language and behavioural skills rapidly occurs (Bell et al., 2016). Physical activity is fundamental in developing a child's motor and cognitive skills. In a systematic review observing the effects of physical activity on motor and cognitive development, it was noted that both domains of development were improved in the presence of activity-based intervention in school-aged children (Zeng et al., 2017).

2.5.1 Effect of Chronic Illness on Development

It is important to consider how the presence of chronic illness may influence both short- and long-term outcomes in infants and children and how this may affect function and quality of life. Chronic illness is any condition that remains present over a prolonged period, requires ongoing medical treatment and intervention, and may be associated with impairments in function and activities of daily living (Bell et al., 2016). Frequent hospitalisation and intervention may disrupt or regress the ability to achieve developmental milestones as physical activity if often limited during hospitalisation. It is important to consider that these children may be admitted frequently, either for recurrent infections or condition-specific management

The impact of chronic paediatric illness on development may differ due to the varying ages of onset and severity of conditions for example Haemophilia A has its greatest impact during early developmental years whilst conditions like Cystic Fibrosis typically have more severe impact in the years after key developmental milestones shave been achieved (Moser et al., 2013). Studies observing HRQOL in children with congenital heart disease have shown that there is often a reduction in physical activity due to limitations associated with the condition such as impaired circulatory systems and fatigue. Frequent absenteeism from school further impacts their neurodevelopment from a cognitive, language and academic skills perspective. Disruption to the

development of these skills may have long-term effects on children with chronic illness as they progress into adolescence and adulthood (Mellion et al., 2014).

2.5.2 Chronic Liver disease and childhood development

Infancy and early childhood are important periods of neurodevelopment from motor through to cognitive functioning. The impact of severe, chronic liver diseases during this period and the effect it can have on neurodevelopment is important to consider (Rodijk et al., 2020; Santos et al., 2021). With the increasing life expectancy of children with CLD after treatment and transplantation, assessing long-term function and quality of life is becoming increasingly important as children reach school-age and adolescence. Some studies have noted deficits in cognition, attention, language and motor skills in children with CLD, with many emphasising the cognitive impairments (Almaas et al., 2015; Santos et al., 2021). In school-aged children attendance is reduced and the presence of hepatic encephalopathy may reduce their performance which can impact their cognitive development (Moser et al., 2013).

Santos et al. conducted a systematic review with meta-analysis in 2020 on the neuropsychomotor development of children and adolescents with liver disease comparing that of children with native liver to those who underwent LT. Twenty-five studies were included with a total of 909 participants with liver disease and 649 underwent LT. The age range of participants was three months to 18 years with sample sizes ranging from 13 participants to 144 over a period from 1988 to 2018. Nineteen studies were conducted with children after LT. For intelligence and cognition versions of the Weschler Intelligence Scales (WISC) were the most commonly used. The following outcome measures were used to measure general, fine motor and gross motor neurodevelopment: Movement Assessment Battery for Children (M-ABC), Mullen Scales of Early Learning (MSEL), Bayley Development Scales, Griffiths Mental Ability Scales (GMDS) and General Development Scale of Minnesota Child Development Inventory (MCDI). Results of the meta-analysis showed that children with liver disease, acute and chronic, present with a deficit in neuropsychomotor development. This improves following LT however, many of the children do not reach neurodevelopment to that of the healthy population. Cognitive development was shown to be low in children with native livers and remained low in those with LT affecting school performance. The review observed that motor development and capacity of

children with liver disease was impaired both pre- and post-transplant (Santos et al., 2021).

Children with CLD, such as Biliary Atresia and Alagille's Syndrome, have many factors that can contribute to developmental deficits. Those presenting with liver disease in the first two years of life are shown to have low neurodevelopmental outcomes as they are exposed to the pathogenicity of hepatic failure in a period of rapid development of the neural system (Santos et al., 2021). Some of these factors are intrinsic to liver disease whilst others are associated with the presence of CLD. Multiple surgeries, frequent hospital admissions, recurrent infections, vitamin deficiency and malnutrition and reduced motor activity can be linked to impaired neurodevelopment (Almaas et al., 2015). Rodijk et al., conducted a study at a centralised centre in the Netherlands demonstrating the long term neurodevelopmental outcomes in children with BA. Tools used to assess motor and cognitive neurodevelopmental outcomes included a validated test battery for the patient as well as parental questionnaires. Study participants included children aged six to twelve years with BA selected using the Netherlands Study group of Biliary Atresia database. Fifty-nine school-aged children between six to twelve years of age were contacted, of which 46 were included, between 2015-2018. Results showed that compared to the Dutch norm population, children with BA showed significantly lower in all domains of neurodevelopment with motor outcomes being the most affected (Rodijk et al., 2020). Almaas et al., conducted a study observing motor competence in children after liver transplantation. Thirty-five children between the ages of four to twelve years who were more than six months post liver transplant were included and tested using the Movement Assessment Battery for Children (M-ABC) from 2007 - 2013. The median age at transplant was six months to two years with testing at median of 5.1 years after transplant. In comparison to healthy control, total M-ABC scores LT children were higher with all sub-scores (manual dexterity, ball skills and balance) scoring worse than the healthy reference group. Seventeen percent of children with LT have significant motor problem, 11% were classified as 'clumsy'. In total, 29% of the children with LT have impaired motor competence compared with 9% in the healthy reference group (Almaas et al., 2015).

When looking at chronic liver disease itself, there are many aspects that can possibly affect development. Severe metabolic dysfunction associated with end-stage liver disease (ESLD) can result in neurotoxic conditions which can impact early development of the brain. Neuromotor damage may be greater in cases when there is

earlier exposure to neurotoxins. However, the neuroplastic ability of a developing brain may be better in cases where the time between onset of disease and transplantation is shorter (Moser et al., 2013; Santos et al., 2021). Hepatic encephalopathy results from an accumulation of neurotoxins such as ammonia which cross the blood-brain barrier which the liver is unable to eliminate (Santos et al., 2021).

Associated malnutrition and growth deficits may be related to possible impairments across motor and cognitive function as well as behavioural aspects. It is also known that persistent sarcopenia in children with liver failure is associated with poor development. Children with ESLD experience constant fatigue which can impact how they perform age-appropriate activities. These children are additionally at high risk for life-threatening complications such as gastrointestinal bleeds (Moser et al., 2013; Takeda et al., 2021). The Childhood Liver Disease Network showed that there are impaired developmental outcomes in infants with BA with the native liver at 12 and 24 months of age (Rodijk et al., 2020). Risk factors for physical and motor delays in children with BA at one and two years of age include older age at the time of KPE or unsuccessful KPE, more than one medical event such as ascites or gastrointestinal bleeding and reduced anthropometric measurements. Physical function can be limited in the presence of abdominal distension associated with ascites (Ng et al., 2018; Santos et al., 2021).

It is important to consider the impact of transplantation on the recovery of neuromotor function and if long-term functional deficits persist.

2.5.3 Critical Illness and development

Advancements in critical care medicine have led to a reduced mortality rate in critically ill patients. However, with increased survival rates subsequent functional impairments may be observed and may persist after hospitalisation (Hlope & Masekela, 2019). It is important to consider the post intensive care outcomes of patients' overall functional status, including both cognitive and motor function, as this can impact quality of life.

It is known that critical illness, especially if associated with multi-organ dysfunction, can lead to muscle atrophy and weakness which can affect patient outcomes. Many patients may develop an ICU-acquired weakness (ICU-AW) as a result of critical illness and prolonged ICU admission influencing progression of illness as well as functional recovery of patients from ICU. Muscle atrophy can occur within five to seven days in

paediatric patients that are critically ill and require mechanical ventilation (Johnson et al., 2018). A retrospective study by Bone et al., demonstrated that there are several factors that can influence functional outcomes for patients admitted in a paeditric Intensive care unit (PICU). These include unscheduled admissions, length of stay, illness severity and risk of mortality status, invasive mechanical ventilation and ECMO. Global functional and cognitive impairments have been associated with the presence of these factors (Bone et al., 2014; Sánchez et al., 2021).

It is important to consider these risk factors when assessing paediatric patients and comparing their post-ICU function with their baseline and how their short- and long-term function and quality of life may be impacted.

2.5.4 Developmental Assessments

The importance of early detection of developmental delay and subsequent early intervention has been emphasised in both term and pre-term infants. Developmental assessments focus on motor function, language, social and cognitive abilities (Alonso, 2008). The American Academy of Paediatrics (AAP) recommends frequent screening using standardised outcome measures to monitor and detect developmental delays and the need for further evaluation and intervention (Schonhaut et al., 2013).

There are a variety of standardised, validated outcome measures available for both clinicians and parents to administer. The Bayley Scales of Infant Development are seen to be the gold-standard in providing a comprehensive assessment of development in children and infants. However, it is not universally applicable, specifically in low to middle-income countries as it is costly, time consuming and requires specific training to administer (Schonhaut et al., 2013). Other outcome measures include the Ages and Stages Questionnaire (ASQ-3), Alberta Infant Motor Scale (AIMS) and Movement Assessment Battery for Children (M-ABC).

2.6 Outcome Measures

2.6.1 Pediatric Inventory of Quality of Life Inventory (PedsQL)

There has been an increase in the development and use of outcome measures to evaluate HRQOL in the paediatric population to improve patient health and wellbeing as well as the impact and value of overall healthcare services. The use of patient-

reported outcome measures (PROM) is increasing to evaluate outcomes and inform clinical decision-making from both patient and family perspectives (Desai et al., 2014; Varni et al., 2011a). The categories of measures include generic and disease specific. Disease-specific measures are argued to be more responsive as they can be used to detect clinical changes and the effects of specific conditions. Generic measures have a wider variety of uses and can be applied to diverse conditions and populations. There are currently over 35 generic measures that can be used in populations younger than 18 years of age with the Pediatric Quality of Life (PedsQL) Inventory 4.0 Generic Core Scale and the EQ-5D-Y being frequently cited in research (Verstraete & Scott, 2022).

The PedsQL is a modular instrument that was developed in 1999 by Varni et al. to measure health-related quality of life (HRQOL) and disease-specific symptoms in children from ages two to 18 years (Demiral et al., 2021; Varni et al., 2011b). It is a patient-reported outcome measure with two components – one from the child's perspective and a parent-proxy version with both addressing the same aspects of QoL (Demiral et al., 2021). It is designed to measure the core dimensions of health set out by the World Health Organisation (WHO), including physical, emotional, and social functioning with the having the addition of school functioning for those over two years of age (Verstraete & Scott, 2022)

PedsQL 4.0 Generic Core Scale

This version of the PedsQL can be administered to children between the ages of two to 18 years and includes self-report questionnaires for children between the ages of five to18 years and parent-proxy questionnaires for children between the ages of two to 18 years. It includes four sub-domains with 15 items: 1) physical functioning, 2) emotional functioning, 3) social functioning and 4) school functioning (Desai et al., 2014). It is scored using a 3-point Likert Scale for the Young Child self-report component (ages 5-7 years) and a 5-point Likert Scale for all other ages included with scores being transformed on a scale from 0-100. The total score is the sum of all the items divided by the number of items answered across all the scales. A higher score indicated an overall perception of a better HRQOL (Demiral et al., 2021).

The PedsQL 4.0 Generic Core Scale has demonstrated good reliability and construct validity in the general and disease-specific populations. It has also demonstrated a response to meaningful change (Desai et al., 2014) .

PedsQL Infant Scale

The PedsQL Infant Scales was designed as a generic HRQOL tool for both healthy and ill infants. The Infant Scales includes two versions for ages 1-12 months and 13-24 months assessing parents' perceptions of the infants overall HRQOL. The 1-12 months version is a 36-item questionnaire assessing five domains: 1) physical functioning, 2) physical symptoms, 3) emotional functioning, 4) social functioning and 5) cognitive functioning. The 45 item 13-24 months version includes the same domains as the 1-12 month version. The format on scoring is identical to the scoring of the Generic Core Scale using a 5-point Likert Scale with higher scores indicating a better HRQOL (Varni et al., 2011a).

As with the Generic Core Scale, the Infant Scale has demonstrated a good construct validity and reliability as well as a responsiveness to meaningful change (Desai et al., 2014; Varni et al., 2011b). Feasibility of the Infant Scales was determined by the percentage of missing values with percentage of missing item responses being 0.7% for both the one to twelve month and the 13-24 month versions (Varni et al., 2011a). The PedsQL Infant Scale reported an alpha coefficient of 0.92 for internal consistency reliability, exceeding the minimum alpha coefficient standard of 0.7 for group comparisons. Discriminant validity was determined using the known-groups method which compares scale scores across groups that are known to differ, in this case healthy infants versus ill infants. Large ranges of effect sizes were noted when comparing healthy infants with chronically ill infants and medium-small rage effect sizes noted when comparing healthy infants with those that are acutely ill, supporting the discriminant validity of the PedsQL Infant Scale (Varni et al., 2011a).

2.6.2 Ages and Stages Questionnaires, Third Edition (ASQ-3)

The Ages and Stages Questionnaire (ASQ-3) was developed for use in screening for development delay in paediatric populations and to determine the need for further evaluation (Rothstein et al., 2017).The tool relies on parent-report to assess the child's progress in each of the five domains. The screening tool can be used in children from one to 66 months of age and includes 21 age-specific questionnaires each with 30 items. Five domains are included: communication, gross motor, fine motor, personal-social and problem solving with items rated from typical development, need for monitoring and need for further evaluation. Each item in the questionnaire is scored as follows: yes (10); sometimes (5) and not yet (0). The ASQ-3 is easy to administer and

can be completed by a professional as well as the caregiver and takes 10-15 minutes to complete (Rothstein et al., 2017).

It has shown to have excellent test-retest reliability with a 92% agreement between caregivers' first and second administration. The interrater and intrarater reliability is shown to be 93% between trained administrators and caregivers. The ASQ-3 has shown to have good validity and reliability as a developmental screening tool and is validated for use in other languages, cross-culturally and in low- to middle-income countries, such as South Africa (Rothstein et al., 2017; A. van Heerden et al., 2017). In a summary of the psychometric properties of the ASQ-3 by Rothstein et al., it was shown to have good content validity. Specificity was determined by correctly identifying risk for developmental delay in 85.9% of children aged 27-36 months and sensitivity was determined by correctly identifying 82.5% of children aged 42-60 months for risk of developmental delay (Rothstein et al., 2017).

2.6.3 Functional Status Score (FSS)

Measuring morbidity status in paediatric populations is becoming increasingly important in research. Decreased mortality associated with the advances of critical care has increased the number of survivors of paediatric ICU. However, this is associated with a significant percentage of survivors experiencing both short- and long-term cognitive, physical, and mental challenges following discharge from the ICU. This has resulted in a shift of focus in health care to consider these functional outcomes (Haque et al., 2022).

Assessing function in large-scale studies can be difficult due to outcome measures being time-consuming and requiring specific training to administer. Another factor to consider when assessing for and using these outcomes is the rapidly changing growth and development in children, therefore developing suitable outcome measures can be challenging (Pollack et al., 2014). Tools used to establish and measure morbidity and functional status in children include the Paediatric Overall Performance Category (POPC), Paediatric Cerebral Performance Category (PCPC) which are qualitative assessments based on the Glasgow Outcome Scale. The POCP and PCPC have been used in multiple studies in the paediatric population and are valid and reliable although several limitations have been noted (Madurga-Revilla et al., 2020; Pollack et al., 2014). These two outcome measures have been used to assess function in survivors of

paediatric ICU and provide an overview of overall and cognitive function. The POCP and PCPC have been validated and have shown associations with gold-standard measures of developments such as the Bayley Psychomotor Developmental Index, the Stanford-Binet Intelligence Test and the Vineland Adaptive Behaviour Scales thus proving them to be valid and reliable outcomes to use amongst paeditric patients (Madurga-Revilla et al., 2020).

The Functional Status Score, FSS, was developed and validated in 2009 by the Collaborative Paediatric Critical Care Research Network (CPCCRN) with the goal of measuring the changing functional status of children during hospitalisation. The scale is based on the principles of the Adaptive Behaviour Assessment System-II Scale (ABAS-II) and of Activities of Daily Living (ADL). It is useful in measuring short-term outcomes of paediatric ICU patients and can be used to compare functional status or the presence of newly acquired impairments from baseline to discharge from the ICU (Haque et al., 2022).

The domains of function assessed include mental status, sensory functioning, communication, motor function, feeding and respiratory status. Scoring is from one (normal functioning) to five (severe dysfunction) with total scores ranging from six to 30. Scores are categorised as follows: normal function (six – seven); mild dysfunction (8-9); moderate dysfunction (10-15); severe dysfunction (16-20) and very severe dysfunction (21-30) (Haque et al., 2022). The FSS correlates well with validated outcomes such as the POCP/PCPC with the advantage of providing more accurate, defined outcomes and increased objectivity across a variety of paediatric ICU patients compared to the POCP/PCPC (Haque et al., 2022; Holding et al., 2021; Madurga-Revilla et al., 2020).

2.7 Conclusion

As improvements in the treatment and management of children with CLD and liver transplantation continue to increase survival rates, the importance for clinicians to assess the impact on overall function and well-being is highlighted. This includes assessing the prevalence of developmental delays as well as HRQOL in children of all ages and the management thereof. On an international scale, multiple studies have been conducting evaluating the HRQOL in paediatric liver transplant recipients and the effect that CLD and transplant may have on a child’s development and overall function.

However, to our knowledge, no such studies have been conducted within the South African context.

Chapter 3 Methods

3.1 Study Design

Longitudinal Cohort Study

A longitudinal cohort study is a type of correlation research which examines a cohort (a group comprising of a shared characteristic) and performs cross-sectional observations over intervals of time. This type of study is typically quantitative research.

This study design is appropriate in this case as we are observing and comparing any changes in the HRQOL and neurodevelopment in children under the age of five receiving liver transplantation. Common characteristics of the cohort will be noted as well as changes over time in the standardised outcome measures.

3.2 Study Setting

WITS Donald Gordon Transplant Unit in Johannesburg, South Africa – Transplant ICU and Paediatric Transplant ward.

The Transplant Unit serves patients from both the public and private sectors and services the whole of South Africa as well as patients requiring living donor transplants from Sub-Saharan Africa.

3.3 Participants

3.3.1 Source of Participants

Wits Donald Gordon Transplant Unit and Transplant Clinic

3.3.2 Sample Size

Thirty-nine paediatric patients were transplanted in 2020 and 25 were transplanted in 2021 with 67% and 60% respectively being under the age of five. In 2020, 56% of patients underwent transplant for Cholestatic disease and only 13% for ALF. In 2021, 48% of transplants were for Cholestatic liver disease. This equates to 15 children in 2020 and 12 children in 2021 under five years with chronic liver failure having a transplant.

Due to the small number of children undergoing liver transplant in South Africa all children who met the inclusion criteria between October 2022 and November 2023 were invited to participate. It was anticipated that a sample of 15-20 participants would be reached.

In the period between January and December 2023, 25 paediatric liver transplants were performed – seven acute liver failure and 18 chronic liver failure. Between October 2022 and November 2023, we obtained consent from 10 children undergoing liver transplant for chronic liver failure under the age of five.

3.3.3 Sample Selection

Children with chronic liver disease, from private or state sector, admitted to Wits Donald Gordon for liver transplant.

3.3.3.1 Inclusion Criteria

- Children and infants under the age of five admitted to Wits Donald Gordon for chronic liver failure awaiting transplant.
- Children undergoing work-up and listed for liver transplantation at Wits Donald Gordon

3.3.3.2 Exclusion Criteria

- Any children admitted to the transplant unit with Acute Liver Failure and requiring a transplant.

3.4 Instrumentation and Outcome Measures

3.4.1 Ages and Stages Questionnaires

ASQ-3 can be administered to children from one to 66 months of age and includes 21 age-specific questionnaires. Five domains are included: communication, gross motor, fine motor, personal-social and problem solving skills with items rated from typical development, need for monitoring and need for further evaluation. Each item in the questionnaire is scored as follows: yes (10); sometimes (5) and not yet (0). The tool takes 10-15 minutes to administer.

AQS-3 has shown to have good test-retest reliability with a 92% agreement between caregivers' first and second administration. The interrater and intrarater reliability is

shown to be 93% between trained administrators and caregivers. Shown to have good content validity, specificity and sensitivity at identifying risk of developmental delay. ASQ-3 has been validated for cross-cultural use (Rothstein et al., 2017; A. van Heerden et al., 2017).

For more detail, refer to section 2.6.2 in the literature review.

3.4.2 Pediatric Inventory of Quality of Life Scale

3.4.2.1 Generic Core Score 4.1

The PedsQL Generic Core Score 4.1 can be administered to children between the ages of two to 18 years and includes self-report questionnaires for children between the ages of five to 18 years and parent-proxy questionnaires for children between the ages of two to18 years. It includes four sub-domains with 15 items.

The tool is cost effective and takes approximately 10-15 minutes to complete.

The PedsQL 4.0 Generic Core Scale has demonstrated good reliability and construct validity in the general and disease-specific populations. It has also demonstrated a response to meaningful change (Desai et al., 2014) .

Refer to section 2.6.2 for more detailed information.

3.4.2.2 Infant Scales

The Infant Scales includes two versions for ages one to 12 months and 13-24 months assessing parents' perceptions of the infants overall HRQOL. The one to 12 months version is a 36-item questionnaire assessing five domains.

The PedsQL Infant Scale reported an alpha coefficient of 0.92 for internal consistency reliability, exceeding the minimum alpha coefficient standard of 0.7 for group comparisons. Discriminant validity was determined using the known-groups method which compares scale scores across groups that are known to differ, in this case healthy infants versus ill infants.

Feasibility was determined by the percentage of missing values with percentage of missing item responses being 0.7% for both the one to twelve month and the 13-24 month versions (Varni et al., 2011a)

The tool is cost-effective and easy to administer, taking approximately 10 – 15 minutes to complete.

Refer to section 2.6.2 for more detailed information.

3.4.3 Functional Status Scale

The FSS is a short-form scale measuring six functional domains – mental status, sensory functioning, communication, motor function, feeding and respiratory status. It is a freely available tool and quick to administer.

Discrimination was very good for moderate and severe dysfunction when compared to the ABAS II categories. It showed intraclass correlations of original and weighted total FSS scores were 0.95 and 0.94, respectively (Pollack et al., 2009).

The FSS correlates well with validated functional outcomes such as POPC and PCPC. For more detailed information refer to section 2.6.2 in the literature review.

3.5 Procedure

1. Paediatric Transplant ward was screened for new patients admitted for chronic liver failure and transplant work-up.
2. Parents/Caregivers of patients meeting the inclusion criteria were informed about the study by the physiotherapist working in the ward and invited to participate. Parents were allowed time to read the information sheet and ask questions before signing consent (Appendices A and B)
3. Pre-transplantation:
    a. Pre-operative demographics and data collection was completed by the researcher.
    b. Functional Status Score (FSS) scored by researcher (Appendix C)
    c. Ages and Stages Questionnaire (ASQ-3) was conducted with caregivers of children younger than 5 and scored by the researcher.
    d. PedsQL questionnaire was administered to parents and scored by the researcher.
4. Post-transplantation:
    a. Generalised ICU assessment was completed day one post-operatively and on discharge from ICU with the relevant data collection sheet being completed. This information was collected by the researcher.
    b. FSS was administered by the researcher to determine the child's functional status in the ICU day one post-operatively, at discharge from ICU and at discharge from the hospital.
    c. During this period, the patients received standard ICU physiotherapy, mobilisation and strengthening.

5. At three-months post-transplantation:
    a. Researcher completed post-transplant data collection, either telephonically or in person when patients returned to WDGMC for the three-month follow-up.
    b. Researcher re-administered ASQ-3 to parents of children under five either in person or telephonically
    c. Researcher re-administered the PedsQL to parents /caregivers to complete in person or telephonically.

3.6 Ethical Considerations

- Permission was obtained from the Research and Ethics Committee at WDGMC prior to commencement of the study (Appendix D)
- Ethics was obtained from the Human Research Ethics Committee (Medical) for Research on Human Subjects, University of the Witwatersrand, prior to the commencement of the research study. (Appendix E)
- Research was commenced only once all ethical clearance was granted.
- The principal investigator was responsible for obtaining all data from participants.
- All data collected is confidential, with only the principal investigator and supervisor having access to the raw data. Data will be stored for six years if not published and for two years if published.
- All data collected was kept anonymous through numbers and coding. The participants were assigned numbers and coded in the data collection table rather than using their names.
- The results were made available to the participants and their caregivers.
- The results will be disseminated by journal publications.
- There was no risk to the participants participating in this study. The participants were able to withdraw from the study at any point. Their withdrawal did not prejudice them in any way.
- The appropriate reimbursement was provided where necessary.
- A distress protocol was in place if w required however no caregivers needed referral for counselling.

3.7 Statistical Analyses

Data was analysed using descriptive statistics and observing change over time. Due to the small sample size only descriptive statistics were used.

Mean and median values were calculated where applicable. Results from initial assessment were compared, when applicable, to values post-operatively and at the three-month follow-up. Mean and median values were used to measure change over time.

Ranges, median and mean values were calculated to analyse length of stay (LoS) in ICU and hospital, number of days ventilated.

Chapter 4 Results

Over a period of 12 months, a total of 10 (n=10) participants who received liver transplantation for chronic liver disease at WDGMC and met the inclusion criteria were recruited. Of the 10 participants, two (n=2) demised post-transplant and one (n=1) was lost to follow-up at three months post-transplant. Seven participants (n=7) were followed up at three months.

Table 4-1 Patient Demographics n=10

Patient Characteristics	**No. (%)**	**Mean, Range**
Male	4 (40)	
Female	6 (60)	
Gestational Age		38.5/40, 29-40

Of the 10 participants four (40%) were male and 6 (60%) were female. Two children were born prematurely, at 29 weeks and 36 weeks respectively of which one child presented with perinatal complications and required Neonatal ICU care. One child had a previous history of a prolonged ICU stay prior to transplantation requiring ventilation. The rest of the participants, to the best of our knowledge, only experienced complications associated with CLD such as portal hypertension, ascites, pruritus and did not have previous ICU admissions.

Table 4-2 Pre-Transplant Clinical Presentation n=10

Patient Characteristics	**No. (%)**	**Mean, Range**
Alagille's Syndrome	2 (20)	
Biliary Atresia	8 (80)	
KPE	6 (60)	
PELD Score n=9	9 (90)	14.13, 4-24
Age at pre-operative assessment (months)	10 (100)	24.25, 9.5-51

PELD score of 9 participants was collected with a mean score of 14.13 and a range of 4 to 24. Eight participants were diagnosed with Biliary Atresia and two with Alagille's Syndrome of which six (60%) underwent KPE.

Table 4-3 Post operative clinical information n=10

Patient Characteristics	No. (%)	Mean, Range
Liver Transplantation	10(100)	
Age at Liver transplantation (months)	10(100)	24.25, 9.5-51
Living Donor	8(80)	
Cadaveric /donor	2(20)	
Days Ventilated	10 (100)	12.2, 1-42
Total LoS (days)	10(100)	30, 9-103+
ICU LoS (days)	10(100)	19.3, 6-48
Ward LoS (days) n=8	8 (80%)	13.62, 2-55+

Mean age at initial assessment and at liver transplant was 24.25 months of age with a range of 9.5 to 51 months of age. Eight of the ten children had living donor transplants while two had cadaveric donors. Mean ICU LoS was 19,3 days with a range of six to 48 days. Mean LoS in the ward was 13.62 days ranging from two to 55 days with one child still admitted at the three-month follow-up. Mean hospital length of stay (LoS) was 30.2 days and a median LoS of 23.5 days.

4.1 Pre-transplant Assessment

4.1.1 Functional Status Score

Pre-transplant Functional Status Score was tallied for all 10 participants with all scoring six out of a possible 30 with the lower score indicating a higher level of function. Every participant scored the lowest possible score for each of the six domains.

4.1.2 Neurodevelopment Assessment

Neurodevelopmental assessment using the ASQ-3 was completed for each participant to assess their pre-transplant development and screen for any developmental delay. Summary of the scores for each category for each participant can be seen in Table 4.4.

Figure 4.1. identifies those delayed, at risk and normal in terms of development for each category of the ASQ-3. Scores were adjusted according to ASQ guidelines for missing answers.

It should be noted that the cut-off ranges for delayed development, at risk and normal development for each domain may differ between age groups.

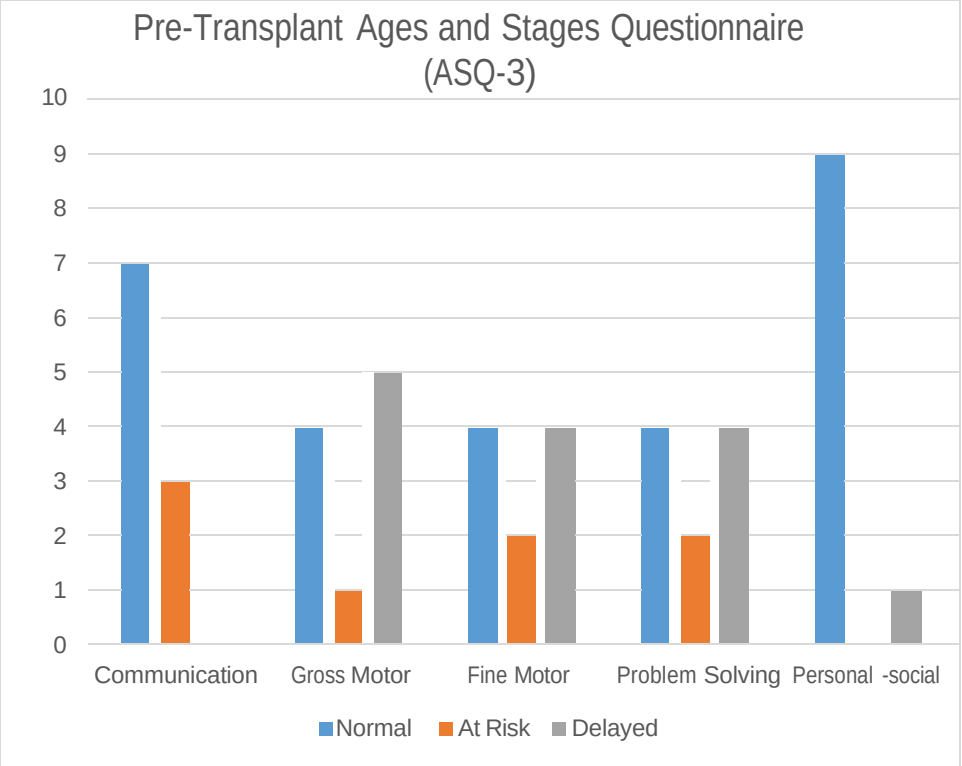

Figure 4-1 *Developmental classification over each category of the ASQ-3 for n=10.*

Communication Skills

Of the 10 children assessed, the mean score was 42 (SD=10.85) out of a possible 60 with the median score of 45. Thirty percent (n=3) were at risk for delay in communication and 70% (n=7) were normally developing in communication skills.

Gross Motor Skills

The mean score for gross motor skills was 32.5(SD=18,59) with a median of 45. Four of the 10 (40%) participants were classified as having normal gross motor skills. One child (10%) with 'at risk' classification and five children (50%) classified as delayed. Scores ranged from lowest at 5/60 to 60/60.

Fine Motor Skills

The mean score out of 60 for fine motor skills was 31 (SD=19.55) and a median of 27.5 with four (40%) classifying as normal, two (20%) classifying as 'at risk' and four (40%) classifying as delayed.

Problem Solving Skills

Mean score for problem solving skills was 30.5 (SD=12.12) and a median of 30. Four (40%) classified as normally developing, two (20%) classified as 'at risk' and four (40%) classified as delayed.

Personal Social Skills

Mean score out of 60 for personal social skills was 43.5 (SD=13.55) and a median of 45, with nine out of ten children classifying as normal and one child classifying as delayed.

Table 4.4 shows a summary of the results for the ASQ-3 for each participant. Results for each category of the ASQ-3 are shown as well as the mean score, median score and standard deviation.

Table 4-4 Pre-transplant ASQ-3 Summary Scores

	Communication /60		**Gross Motor /60**		**Fine Motor /60**		**Problem Solving /60**		**Personal Social /60**	
A	55	Normal	25	At Risk	50	Normal	40	Normal	45	Normal
B	25	At Risk	50	Normal	40	Normal	30	At Risk	50	Normal
C	55	Normal	30	Delayed	15	Delayed	40	Normal	45	Normal
D	45	Normal	60	Normal	20	At Risk	25	Delayed	40	Normal
E	45	Normal	50	Normal	60	Normal	40	Normal	40	Normal
F	40	At Risk	20	Delayed	15	Delayed	10	Delayed	55	Normal
G	45	Normal	5	Delayed	5	Delayed	20	Delayed	10	Delayed
H	35	Normal	15	Delayed	35	At Risk	20	Delayed	50	Normal
I	25	At Risk	50	Normal	15	Delayed	30	At Risk	40	Normal
J	50	Normal	20	Delayed	55	Normal	50	Normal	60	Normal
Mean Scores	**42**		**32.5**		**31**		**30.5**		**43.5**	
Median	**45**		**27,5**		**27,5**		**30**		**45**	
Standard deviation	**10,85**		**18,59**		**19,55**		**12,12**		**13,55**	

4.1.3 Health-related Quality of Life

Scores of the PedsQL Infant Scales and Generic Core Score 4.0 were calculated for each participant, with higher scores indicating higher quality of life. Summary scores are represented in the Table 4.5. Physical health summary score includes physical

function and physical symptoms, and the psychosocial summary score includes emotional, cognitive, and social function as well as school function where applicable. Mean values of summary score and total scores are recorded in Table 4.5. It was noted that none of the children attended creche or school.

Figure 4.2 indicates the scoring each participant under two years of age using the PedsQL Infant Scale.

Figure 4.3 indicates the scores of those between two to four years of age using the Generic Core Score 4.0.

Physical Function

Mean score across participants for physical function was 77.74 with scores ranging from 43.75 to 100. Median score of 76.39 and standard deviation (SD) of 18.66.

Physical Symptoms

This domain is included only in the Infant Scales (n=5).

Mean score across participants for physical symptoms was 90.47 with a median score of 91.25 (SD=7.97) and a range of 80 to 100

Emotional Function

Mean score for emotional function was 72.38 with score ranging from 52 to 90. Median score of 74.58 (SD=12.98).

Cognitive Function

Cognitive functioning is only included in the Infant Scales. Mean score across participants was 91.20 with scores ranging from 75 to 100. Median score was 97.2 and a SD of 11.71.

Social Function

Mean scores for social function across all participants was 87.88 with scores ranging from 43.75 to 100 and a median score of 100 and SD of 19.20.

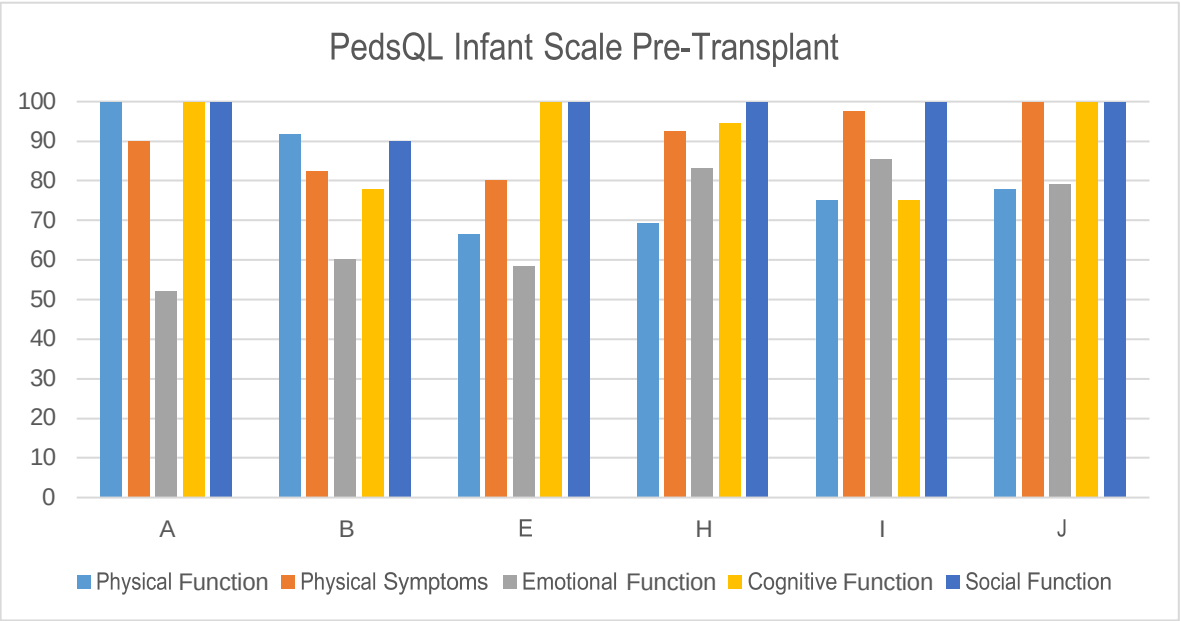

Figure 4-2 *Scores of each domain out of 100 for participants between 1-24 months of age. (n=6)*

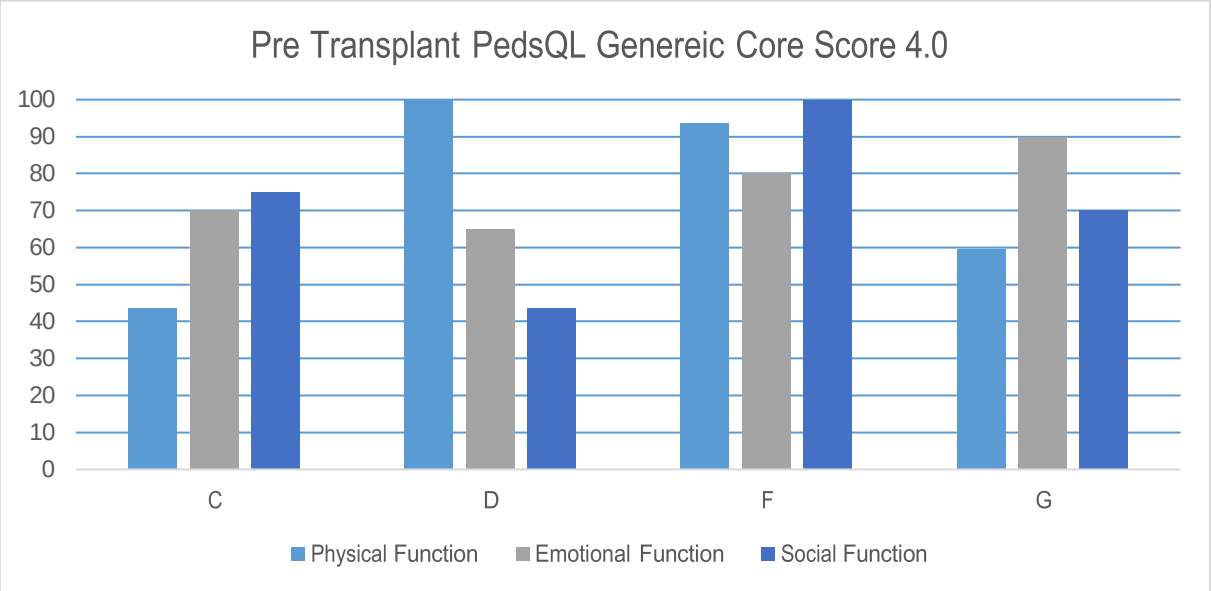

Figure 4-3 *Scores of each domain out of 100 for participants between two to four years of age (n=4)*

Table 4-5 Physical and Psychosocial Health Summary Scores of PedsQL

	Physical health summary score	Psychosocial health summary score	PedsQL Total Score
A	94,74	77,88	**85**
B	86,84	72,12	**78,33**
C	43,75	72,5	**59,72**
D	100	55,56	**68,42**
E	75	75	**75**
F	93,75	90	**91,67**
G	59,38	80	**70,83**
H	81,58	90,38	**86,67**
I	86,84	69,23	**76,66**
J	89,47	90	**89,77**
Mean	**81,135**	**77,267**	**78,207**
SD	**17,469**	**11,026**	**10,206**
Median	**86,84**	**76,44**	**77,495**

4.2 Post-transplant Assessment

The FSS was assessed on day one post-transplant for all participants (n=10) with a mean score of 16.9 (SD=7.81) and median score of 15.5. Scores ranged from eight to twenty-nine out of thirty with higher scores indicating a lower functional status. Eight of the ten children were ventilated on initial assessment day one post-transplant.

Table 4.3 summarises the post-operative clinical presentation.

Table 4-6 FSS and Glascow Coma Scale Scores Day 1 post-operatively

	FSS /30	**GCS /15**
A	24	2
B	9	15
C	9	10
D	29	2
E	8	15
F	26	2
G	15	2
H	11	10
I	16	6
J	22	6
Mean	**16.9**	**7**
Standard Deviation	**7.81**	**5.25**
Median	**15.5**	**6**

Eight participants were discharged from intensive care to the ward (n=8) and two participants demised due to complications (n=2) during the post-operative period with LoS of 42 and 34 days respectively. Mean ICU LoS was 19,3 days with a range of six to 48 days. Mean LoS in the ward was 13.62 days ranging from two to 55 days. Mean hospital length of stay (LoS) was 30.2 days and a median LoS of 23.5 days. On discharge to the ward, three (n=3) children required additional oxygen support.
Mean FSS on discharge to the ward was 6.38 (SD=0.5).
Days ventilated and LoS are summarised in Table 4.7.

Of the eight children admitted to the ward, all were discharged from hospital except one participant still admitted at time of completion of the study with LoS in hospital >100 days. At discharge from hospital (n=8), all children were vitally stable and on room air. All eight children scored six on the FSS at discharge.
All participants received standard post-operative physiotherapy in the ICU and ward.

Table 4-7 Summary of Hospital LoS and days ventilated.

Patient	Days spent in ICU	Days ventilated	Days in ward
A	24	11	10
B	8	1	3
C	6	1	22
D	42	42	-
E	6	1	4
F	34	34	-
G	6	2	3
H	48	26	>55
I	9	2	10
J	10	2	2
Mean	19.3	12.2	13.62
Standard deviation	16.4	15.8	17.9
Median	9.5	2	7

4.3 Follow-up Assessment

Follow-up ASQ-3, PedsQL and FSS were completed at three months post-transplant for a total of seven participants (n=7). One child was lost to study follow-up (n=1). Mean age at follow-up assessment was 23.5 months with a range of 12 to 35 months of age. One child (n=1) was still admitted to the ward at the three month follow up.

4.3.1 Functional Assessment

Follow-up FSS was completed for all seven remaining participants (n=7). Mean score was 6.7, SD of 0.38 and a median score of 6.

Table 4-8 FSS Scores /30 at three months post-transplant

A	6
B	6
C	6
D	- demised
E	6
F	- demised
G	6
H	7
I	- lost to study follow-up
J	6
Mean	**6.14**
Standard Deviation	**0.36**
Median	**6**

4.3.1.1 Comparison of FSS

As shown in Figure 4.4 we note that the FSS results were consistent across all participants on initial assessment. An increase in scores, indicating a lower functional status, was seen in the immediate post-transplant period. This is mainly as a result of mechanical ventilation and requirement of respiratory support as well as sedation post-operatively.

On discharge from ICU to the ward, on discharge from hospital and at three month follow-up, we can note that the FSS scores return to baseline scores.

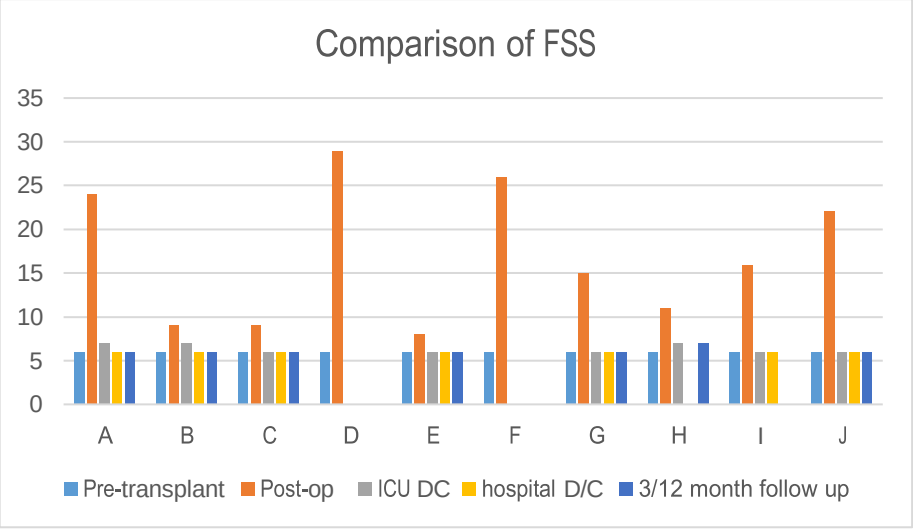

Figure 4-4 *Comparison of FSS scores for all participants from pre-transplant to three-month follow up*

4.3.2 Neurodevelopment

ASQ-3 was completed at a three month follow up for seven remaining participants (n=7). **Figure 4.5** shows the comparison of each domain for all seven participants. It is important to note that categories may differ in terms of ranges to determine classification.

Table 4.9 shows the summary of the ASQ-3 results for each child.

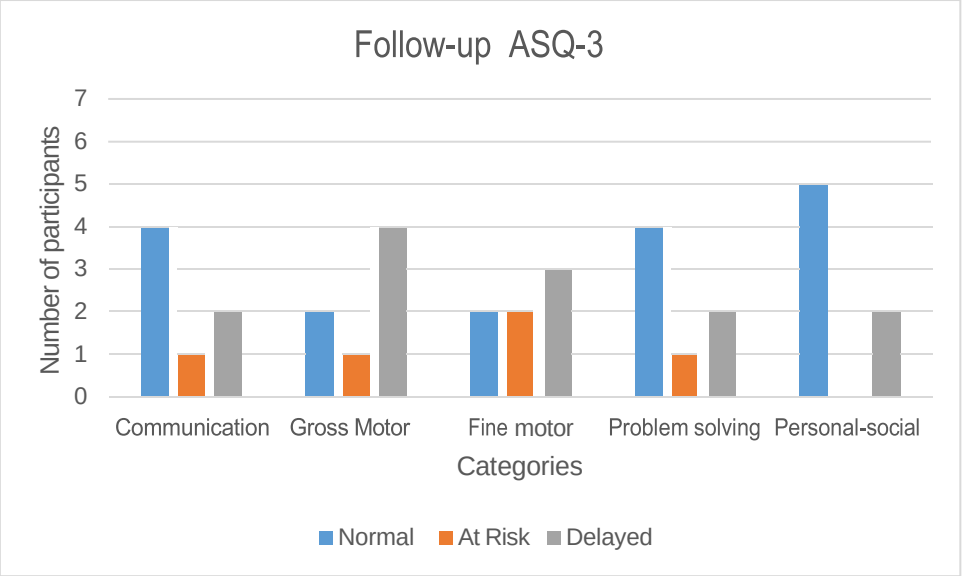

Figure 4-5 *The number of children categorised as "normal", "at risk" and "delayed" in each domain of the ASQ-3*

Communication Skills

Mean score across the seven participants was 40.17 (SD=14.84) with a median score of 40. Four children (57%) classified as normally developing, one child (14%) classified as at risk and two children (28.5%%) scored classified as delayed.

Gross Motor Skills

Mean score across n=7 was 32.14 (SD=20.18) with median score of 35.

Two children (28.5%) classified as normally developing, one child (14%) classified as at risk and four children (57%) classified as delayed.

Fine Motor Skills

Mean score across the seven participants was 30 (SD=18.71) with a median score of 35. Two children (28.5%) classified as normally developing and two (28.5%) classified as at risk for developmental delay. Three children (42.8%) classified as developmentally delayed.

Problem Solving Skills

Mean score for n=7 was 37.86 (SD=12.86) and a median score of 30.

Four participants (57%) classified as normally developing, one child (14%) classified as at risk for developmental delay and two children (28.5%) classified as developmentally delayed.

Personal Social Skills

Mean score across participants (n=7) was 37.14 (SD=11.13) and a median of 40.

Five children (71%) classified as normally developing and two children (28.5%) classified as developmentally delayed.

Table 4.9 shows the summary of the ASQ-3 results for each child.

Table 4-9 Follow-up ASQ-3 Summary Scores (n=7)

	Communication /60		**Gross Motor /60**		**Fine Motor /60**		**Problem Solving /60**		**Personal Social /60**	
A	30	At Risk	35	Delayed	40	At Risk	60	Normal	45	Normal
B	50	Normal	35	At Risk	35	At Risk	50	Normal	40	Normal
C	30	Delayed	30	Delayed	10	Delayed	30	Delayed	30	Delayed
E	55	Normal	60	Normal	55	Normal	40	Normal	40	Normal
G	40	Normal	15	Delayed	5	Delayed	30	Normal	45	Normal
H	20	Delayed	0	Delayed	20	Delayed	25	Delayed	15	Delayed
J	60	Normal	50	Normal	45	Normal	30	At Risk	45	Normal
Mean Scores	**40,71**		**32,14**		**30**		**37,86**		**37,14**	
SD	**14,84**		**20,18**		**18,71**		**12,86**		**11,13**	
Median	**40**		**35**		**35**		**30**		**40**	

4.3.2.1 Comparison of Neurodevelopment

Table 4.10 shows a comparison for ASQ-3 for each participant on initial assessment pre-transplant and at the three month follow-up.

Communication skills improved or remained the same in four of the seven remaining participants. Three children regressed in terms of their communication skills. Of those that regressed, Child A and Child H both had prolonged periods of ventilation and prolonged ICU LoS as represented in Table 4.7.

Gross Motor skills were delayed in five children on initial assessment. Of the seven children assessed at follow-up, one child showed an improvement in gross motor skills from delayed to normal. Two regressed from at risk and normal to delayed and at risk respectively whilst three remained delayed and one child maintained normal gross motor skills. Of those delayed at three month follow up, child A and H, two had increased hospital LoS as seen in Table 4.7.

Fine motor skills were delayed in four participants on initial assessment, normal in four participants and at risk in two participants. Two children regressed from normal to at risk. One child regressed from at risk to delayed, two maintained normal development and two remained delayed at three months post-transplant.

Problem solving skills on initial assessment were delayed in four children, at risk in one child and normal in five children. At assessment three months post-transplant, two children regressed from normal to delayed and at risk respectively. Two children showed improvement from at risk and delayed to normal development. Two children maintained normal development and one remained delayed.

Personal social skills were normal in nine of the ten children and delayed in one child. At three month follow-up assessment post-transplant, two children regressed from normal to delayed development, one child showed improvement from delayed to normal development and four maintained normal development.

Table 4-10 Comparison of Pre- and Three month post-transplant ASQ-3 results

	Communication		Gross Motor		Fine Motor		Problem Solving		Personal Social	
	PRE	**POST**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**
A	Normal	At risk	At risk	Delayed	Normal	At risk	Normal	Normal	Normal	Normal
B	At risk	Normal	Normal	At risk	Normal	At risk	At risk	Normal	Normal	Normal
C	Normal	Delayed	Delayed	Delayed	Delayed	Delayed	Normal	Delayed	Normal	Delayed
D	Normal	-	Normal	-	At risk	-	Delayed	-	Normal	-
E	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
F	At risk	-	Delayed	-	Delayed	-	Delayed	-	Normal	-
G	Normal	Normal	Delayed	Delayed	Delayed	Delayed	Delayed	Normal	Delayed	Normal
H	Normal	Delayed	Delayed	Delayed	At risk	Delayed	Delayed	Delayed	Normal	Delayed
I	At risk	-	Normal	-	Delayed	-	Normal	-	Normal	-
J	Normal	Normal	Delayed	Normal	Normal	Normal	Normal	At risk	Normal	Normal

4.3.3 Quality of life

PedsQL assessment was completed at three month follow-up. Physical health and psychosocial health summary of scores for participants (n=7) are recorded in Table 4.8.

Figure 4.6 shows follow-up scores in each domain for participants under two years of age using the PedsQL Infant Scale.

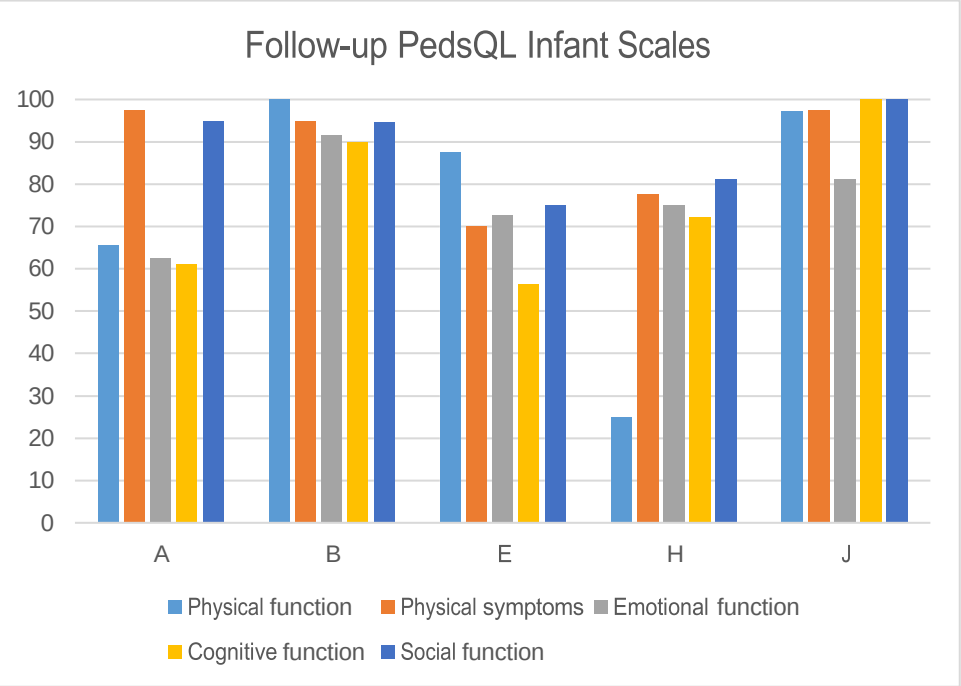

Figure 4-6 *Follow-up scores out of 100 for n=5 for the PedsQL Infant Scale*

Figure 4.7 shows the results of participants between two to four years of age using the PedsQL Generic Core Score 4.0.

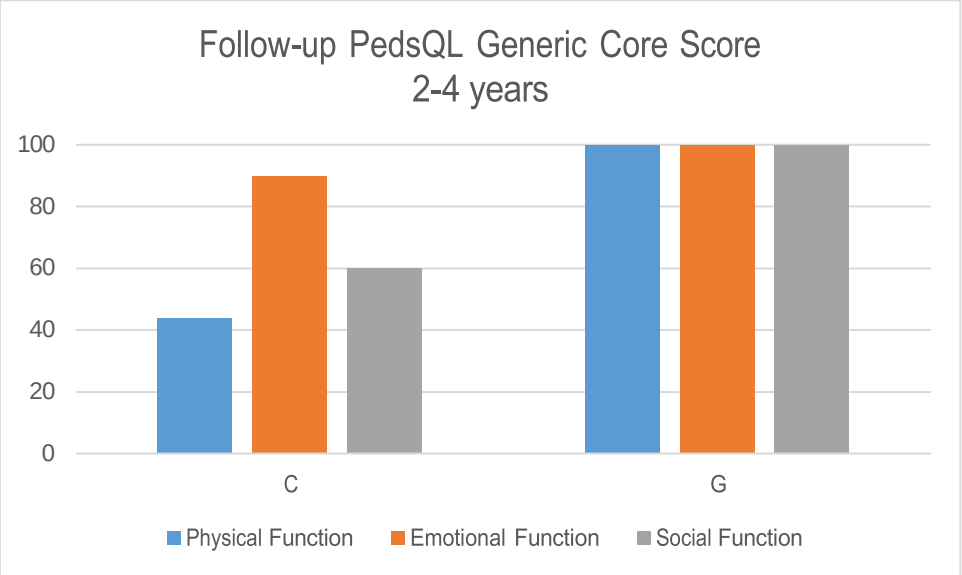

Figure 4-7 *scores out of 100 for n=2 for PedsQL Generic Core Score 4.0 for participants between 2-4 years of age*

Physical Function

Mean score across the participants (n=7) was 74.15 (SD=30.16). Scores ranged from 25 to 100. Median score was 87.5.

Physical Symptoms

Mean score for physical symptoms in the Infant Scale across the five children under 24 months of age was 87.5 (SD=12.87) with a range of 70 to 97.5. Median score 95.

Emotional Function

Mean score across all seven participants in the Infant Scale and Generic Core Score was 81.89 (SD=12.89) with score ranging from 62.5 to 100. Median score for emotional function was 81.25.

Cognitive Function

Mean score for cognitive function for children (n=5) in the Infant Scale was 75.92 (SD= 18.69) with scores ranging from 56.25 to 100. Median score for the sample was 72.22.

Social Function

Mean score across the seven participants for social function was 86.52 (SD=15.06). Scores ranged from 60 to 100. Median score 94.44

Table 4-11 Summary Scores of PedsQL

	Physical health summary score	Psychosocial health summary score	Total
A	83,33	68,27	**74,43**
B	97,37	92,31	**94,44**
C	43,75	75	**61,11**
E	76,56	70	**72,92**
G	100	100	**100**
H	52,63	75	**65,34**
J	97,27	91,35	**93,89**
Mean	**78,70**	**82,82**	**78,70**
SD	**22,63**	**13,38**	**22,63**
Median	**83,33**	**83,175**	**74,43**

4.3.3.1 Comparison of Pre- transplant and three month post-transplant PedsQL

Physical Health Summary Score, seen in Table 4.11, improved in three children, remained the same in one child and reduced in two children, both with prolonged hospital LoS, when comparing pre-transplant scores and three month follow-up scores. The greatest improvement was seen in participant G from a score of 59.38 to 100.

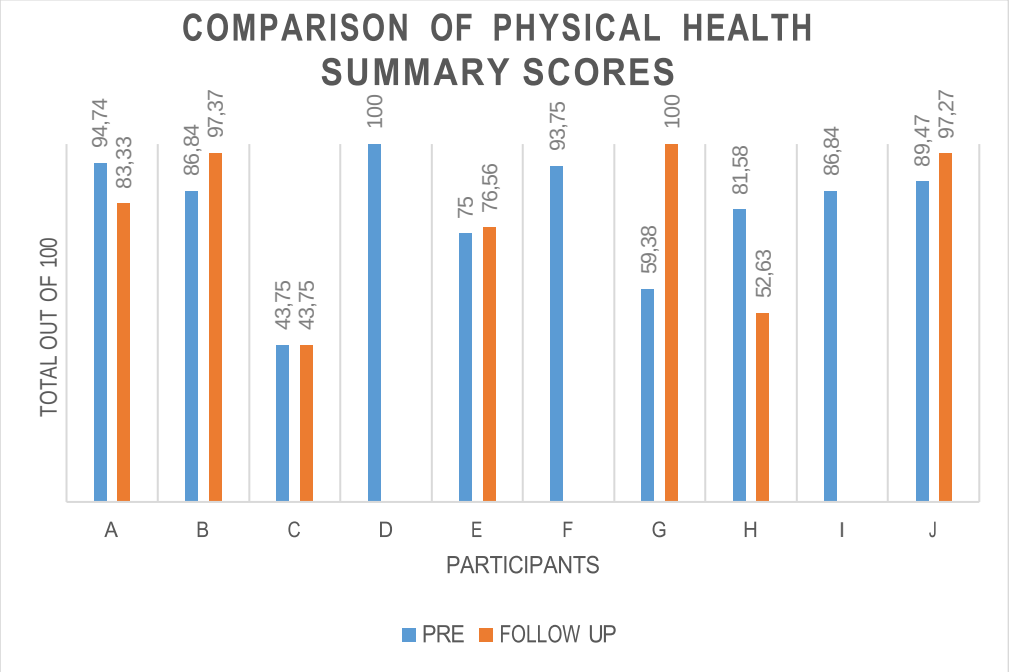

Figure 4-8 *Comparison of PedsQL Physical Health Summary scores for each participant pre-transplant and at three month follow-up assessment.*

Psychosocial Health Summary Score, seen in Table 4.11, improved in four children with the greatest improvement seen in participants B and G. Scores reduced in three children. Of those that showed a decreased HRQOL, two children had prolonged LoS in ICU and hospital.

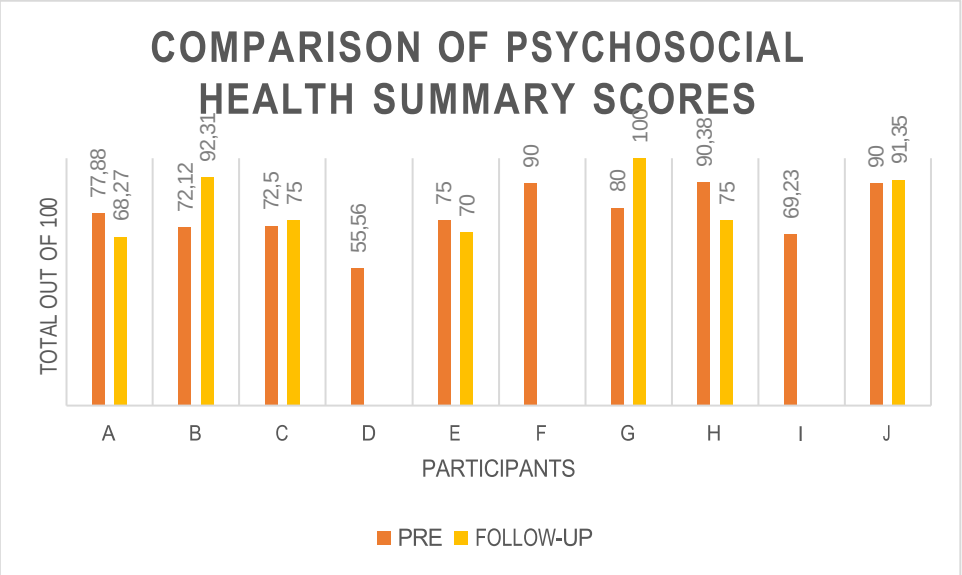

Figure 4-9 *Comparison of PedsQL Psychosocial Health Summary score for each participant pre-transplant and at three month follow-up.*

Comparison of PedsQL Total scores are seen in Figure 4.9. Overall HRQOL as represented from PedsQL improved in four children with the greatest improvement seen in participant G. Scores were reduced in three children, two of which had prolonged hospital LoS, when comparing pre-transplant and three month follow-up results.

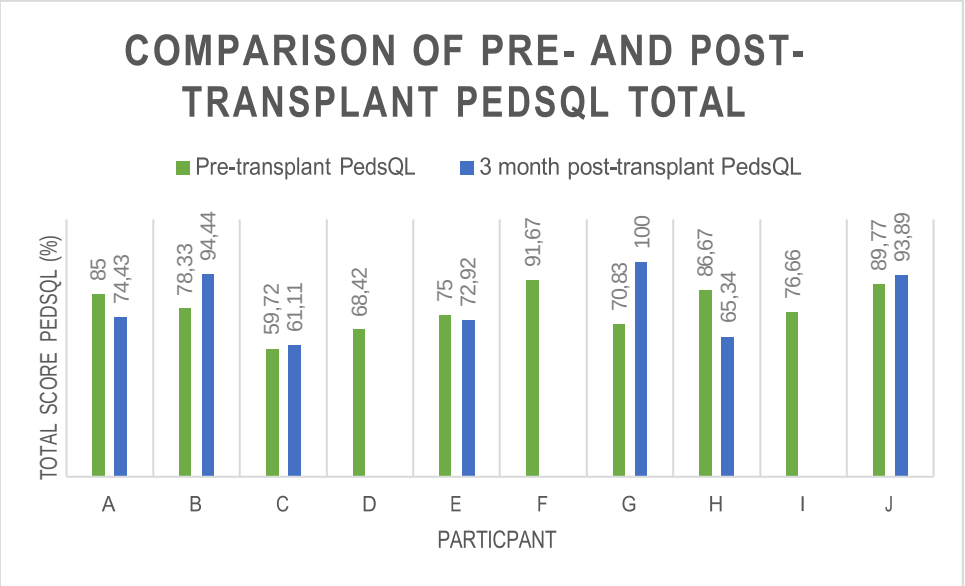

Figure 4-10 *Comparison of pre-transplant and three-month follow up total PedsQL scores for each participant.*

Results will be further discussed in Chapter 5.

Chapter 5 Discussion

5.1 Demographics

This study included ten children, of which four were male and six were female, under the age of five years undergoing liver transplant for CLD. Eight were diagnosed with Biliary Atresia and two with Alagille's Syndrome. The mean age of the children was 24 months. A study conducted by Rodijk et al., observing the long term neurodevelopmental outcomes in 49 children, of which 36 had undergone liver transplantation, with Biliary Atresia between ages of six to 12 years. The inclusion period was from 2015 to 2018 (Rodijk et al., 2020). Almaas et al., conducted a cross-sectional study observing impaired motor competence in 35 children between the ages of four to 12 years with transplanted liver. The recruitment period spanned from 2007 to 2013 (Almaas et al., 2015). Ng et al., conducted a prospective, longitudinal multicentre study observing neurodevelopmental outcomes in children at 12 months and at 24 months with Biliary Atresia with native livers. Study period spanned from 2004 to 2012 (Ng et al., 2018). A systematic review by Santos et al., reviewing observational studies between 1980 and 2019 on the effects of liver disease on neuropsychomotor development of children and adolescents both with native liver and those with liver transplantation. Ages across the 25 studies meeting the inclusion criteria six months up to 18 years (Santos et al., 2021). In comparison to similar studies observing neurodevelopmental outcomes of children with liver disease our study sample is smaller and our participants were younger. However, our period of data collection spanned a shorter length of time of only one year compared to other studies.

5.2 Functional Status

Functional status as measured by the FSS pre-transplant was consistent across all participants, all scoring the lowest possible score indicating a high functional status.

FSS scores across all participants were higher in the immediate post-operative period, primarily due to ventilation requirements, sedation and post-operative feeding status indicating a lower functional status in ICU. A comparison of FSS scores from pre-transplant, during hospital admission and at three month follow up is shown in Figure 4.4. At three month follow-up, all but one child returned to baseline function according to the FSS. Child H had a score of seven out of 30 and was still admitted to the ward.

A systematic review by Sanchez et al., measuring global function after paeditric ICU admission using the PCPC and POPC showed a similar relationship between global function and LoS and risk of mortality (Sánchez et al., 2021).

5.3 Neurodevelopment

This study aimed to determine the presence of neurodevelopmental delays in children with chronic liver disease under five years awaiting transplant, both with and without KPE, as well as at three-months post liver transplant. Using the ASQ-3, neurodevelopment was assessed and compared pre-liver transplant and at three months post-transplant for a study sample of ten children under five years of age.

5.3.1 Pre-transplant Neurodevelopment

We noted delay in gross motor (50%), fine motor (40%) and problem solving skills (40%) in children with chronic liver disease with native liver and awaiting transplantation. Communication and personal-social skills showed a high percentage of normal development, 70% and 90% respectively. Of the two participants with ALGS, gross motor was significantly delayed in one and at risk in the other. Of the eight participants with Biliary Atresia, developmental delay was shown in gross motor skills (40%), fine motor skills (37.5%) and problem solving skills (37.5%). Overall, gross motor, fine motor and problem solving showed the highest frequency of developmental delay across all participants. This could be in line with the presence of cholestasis as well as undergoing major surgery in the case of KPE. Six of the eight participants with BA underwent KPE. Major surgery in infants and children is a possible risk factor for impairments in neurodevelopment (Rodijk et al., 2020). The presence of cognitive delays in children with chronic liver disease is also associated with the presence of chronic hepatic encephalopathy (Santos et al., 2021). In a multicentre study by Ng et al., assessing neurodevelopmental outcomes in BA with native liver, it was determined that even in the presence of KPE, children with BA between one and two years of age were at increased risk for neurodevelopmental delays (Ng et al., 2018). The presence of conditions associated with advanced liver disease such as ascites, malnourishment and growth delays are factors that can all affect motor development (Ng et al., 2018). A systematic review by Santos et al., showed that children with hepatic failure in the first two years of life are exposed to neurotoxic pathogens such as ammonia and other sequalae of hepatic failure in a period of rapid development which results in lower

neurodevelopmental scores (Santos et al., 2021). This study underlies the importance of assessment and intervention for developmental delay, specifically neuromotor delay, in children with chronic liver disease even before they may qualify for a liver transplant.

Post-Transplant Neurodevelopment

At three months post-transplant, neurodevelopment was assessed in the seven children remaining in the study. Overall, delay was present across all domains: communication (28.5%), gross motor (57%), fine motor (42%), problem solving (28.5%) and personal social skills (28.5%). A comparison for each child's initial assessment and post-transplant assessment can be seen in Table 4.10. Child A showed deterioration in communication (normal to at risk), gross motor (at risk to delayed) and fine motor (normal to at risk) but showed improvement in problem solving skills. It was noted that Child A had a prolonged ICU stay and hospital LoS. Child B showed deterioration in gross motor (normal to at risk) and fine motor skills (normal to at risk) but showed improvement in communication (at risk to normal) and problem solving skills (at risk to normal). Child C showed deterioration in communication, problem solving and personal social skills from normal to delayed and remained delayed in gross motor and fine motor skills. Child C sustained a pathological fracture in the lower limb during the three month post-operative period as well as a prolonged stay in the ward post ICU discharge. It should be noted that Child C was not attending creche or school at the three month follow-up. Child E maintained normal development across all domains. Child G showed improvement in problem solving and personal social skills from delayed to normal but remained delayed in gross and fine motor skills. However, it was noted that the score for gross motor, despite remaining delayed, improved. Child H showed deterioration and was delayed across all domains with gross motor skills scoring the lowest. It should be noted that Child H had a prolonged period of ventilation, increased LoS in ICU and was still admitted to the ward at the time of three month follow-up. Child J showed improvement in gross motor skills from delayed to normal and deterioration in problem solving skills from normal to at risk.

It is important to note that although liver transplant has improved patient survival, studies have shown that many children with transplanted liver present with cognitive impairments The presence of delayed in problem solving skills and communication skills in so, associated with cognitive functioning, is in line with research showing cognitive skills remain low after liver transplantation (Østensen et al., 2022; Santos et

al., 2021). A cross-sectional study by Almaas et al, observing motor competence in children who underwent liver transplant determined that 29% of children presented with impaired motor abilities compared to healthy norms (Almaas et al., 2015). This is in line with our findings. However, it is important to note that we have a short follow-up period compared to other studies and that further studies with longer follow-up are recommended.

In addition to the effects of liver transplant on neurodevelopment, it is important to consider the effects of ICU admission on development. A systematic review by Sanchez et al., on impact of paediatric ICU admission on cognition and global functioning of patients. Four studies found a relationship between ICU LoS and cognition. Factors identified and associated with worsening cognitive and global function post ICU stay included: LoS of more than two days, mechanical ventilation and unscheduled admission to ICU, increased mortality rate and invasive interventions (Sánchez et al., 2021).

5.4 Quality of Life

An objective of this study was to determine the HRQOL in children with chronic liver disease under five both pre- and post-liver transplantation using the PedsQL Infant Scale and Generic Core Score 4.0. Comparison of pre- and post-transplant results can be seen in figure 4.10.

Pre-transplantation emotional function followed by physical function showed the lowest mean and median scores across all participants. This is in line with previous research showing HRQOL is reduced in infants and children with chronic liver disease. Mohammad et al., examined HRQOL using the PedsQL Infant scales and determined that infants with chronic liver disease had significantly lower HRQOL in comparison to healthy controls. This was associated with recent hospitalisations and presence of adverse effects of liver disease such as ascites (Mohammad et al., 2016). Common concern amongst caregivers was the presence of pruritus however this symptom is not included in the PedsQL but it is an important factor to consider when observing overall QoL.

HRQOL at three month post liver transplant was compared to pre-transplant results. In three of the seven remaining participants, it is interesting to note that the total score for HRQOL was less than the pre-transplant score. Observing physical health summary score, mean score was lower than that of the pre-transplant score. However, the mean psychosocial summary score and mean total score were higher than pre-transplant scoring indicating an overall improvement in HRQOL. It is important to note that HRQOL in transplant recipients is still shown to be lower than that of healthy controls (Sorensen, 2016).

Although improvement could be seen in some children in developmental domains and HRQOL, it is important to consider those that regressed in terms of development or remained at risk and delayed as well as those whose HRQOL scores reduced post-transplant and the causes thereof. From this study, the importance of early and continued intervention both pre- and post-liver transplant in children with chronic liver disease is highlighted to aid in preventing or improving developmental delay as well as intervening to improve aspects of quality of live where able.

Chapter 6 Conclusion and Recommendations

Conclusion

Minimal research has been conducted in the South African context on the impact of chronic liver disease and liver transplant on neurodevelopment and HRQOL in young children and infants. Chronic liver disease is a complex condition with various medical sequalae. The aim of this longitudinal cohort study was to determine and compare neurodevelopment, global function and HRQOL on children under five years of age undergoing liver transplant for chronic liver disease pre-operatively and in the short-term follow-up period of three months.

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In keeping with previous research on HRQOL in children with chronic disease this study showed that some aspects of HRQOL, particularly in physical domains, may be further reduced in the post-transplant follow-up period. HRQOL is therefore an important factor to consider when evaluating infants and children with chronic liver disease both with native and transplanted liver as well as HRQOL in long-term follow-ups.

The impact of chronic liver disease and transplant on neurodevelopment was assessed. Although results differed amongst participants, and considering the small sample size, it was found that gross motor, fine motor and problem solving skills showed a higher number of impairments across participants pre-liver transplant. At the three-month follow-up, those with a prolonged ICU and hospital LoS showed greater impairments across developmental domains. There is a risk of deterioration in developmental skills post-operatively.

In conclusion, chronic liver disease and liver transplant may impact both HRQOL and neurodevelopment in children under the age of five. Due to the risk of impaired neuropsychomotor development, early intervention and post-operative intervention is recommended. Further studies are recommended to determine long-term outcomes.

6.1 Clinical/Practical Recommendations

- Pre-transplant developmental screening of all children with chronic liver disease
- Post-operative neurodevelopmental assessments and intervention as required.
- Co-ordination of services across facilities and disciplines to avoid children being lost to follow-up and not receiving intervention for complex and varied health and rehabilitation needs.
- Multidisciplinary involvement as children presented with delays across multiple domains of development and HRQOL.

6.2 Recommendation for Future Research

To our knowledge this is the first study of its kind assessing the HRQOL and neurodevelopment in children with Chronic Liver Disease in South Africa. Recommendations for future research include a longer follow-up period to assess long-term outcomes and to compare any changes over time.

Future research could include the population of those children with acute liver failure receiving transplant and the comparison on HRQOL and to compare neurodevelopment between healthy populations, CLD and ALF patients.

Further research on the long-term neurodevelopmental and quality of life outcomes in children post-liver transplant is recommended, including following children into school-age.

Research on the effects of a physiotherapy or neurodevelopmental therapy, including occupational therapy, should be considered to determine if there are significant benefits to early neurodevelopmental interventions.

6.3 Strengths and Limitations

Limitations of the study included a limited sample size due to the small patient population as well as being a single-centre study. As South Africa has diverse socioeconomic and cultural practices, elements of the outcome measures were not

always applicable, and the caregivers had not exposed the children to certain activities. Overcoming language barriers was a challenge however translators were used when available. Face-to-face follow-up with participants was challenging due to a portion of the participants belonging to the public sector and a separate transplant clinic as well as patients receiving transplants coming from various regions of South Africa. Therefore, we mainly relied on telephonic follow-up.

Although small, this study presents unique insights into the developmental challenges of young children in South Africa living with chronic liver disease. The multiple assessment points and in depth assessments have provided as yet undocumented information on quality of live and neurodevelopment of these children over a critical time period in their health journey.

The results of this study will assist in putting measures in place to ensure children with chronic liver disease not only survive but thrive.

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Appendices

Appendix a Parent Information Sheet

The developmental and functional outcomes in children with chronic liver disease undergoing liver transplant; a longitudinal cohort study.

Dear Parent,

Thank you for taking the time to read this letter.

We, Prof. Joanne Potterton and Kyara Reynhardt, are physiotherapists doing research children undergoing liver transplantation. Research is a process used in seeking new knowledge. In this study, we want to determine the functional and developmental outcomes of children with chronic liver disease undergoing liver transplant.

We are inviting your child to participate in the research study. The study will take place at Wits Donald Gordon Medical Centre within the Transplant Unit, with research being conducted by myself, Kyara Reynhardt as well as qualified physiotherapists working at WDGMC within the unit.

The purpose of the study is to determine the functional abilities of your child and the presence of any developmental delays that may be present in children with Chronic Liver Disease. We would like to assess your child pre-operatively when they are admitted to the ward for work-up for transplant, again in the ICU post-operatively, 3 months post-transplant and again at six months and one year post-transplant.

The pre-operative assessment includes two questionnaires, the Ages and Stages Questionnaire (ASQ-3) and the Paediatric Quality of Life Inventory (PedsQL). The ASQ-3 is a screening tool to assess your child's development. It includes simple questions and can be done telephonically or in person. This screening tool will highlight areas of strengths and weaknesses or areas of concern regarding your child's development. It will take approximately 15-20 minutes to complete with the physiotherapist. We will assess your child with the ASQ-3 pre-operatively and again at three-months, six-months, and 12-month post-transplant. The PedsQL is a questionnaire that helps to assess the Health-related Quality of Life for your child. We use it to help detect any areas that your child might be struggling with and assess how this can affect your child's overall quality of life. Again, it is a simple questionnaire and can be completed in person or telephonically by the parent and will take no longer than approximately 20-30 minutes. We will assess your child with the PedsQL pre-

operatively and again three, six and 12-months post-transplant and compare any differences in the quality of life.

Once your child has received the liver transplant, we will carry out our routine ICU physiotherapy assessment and complete a Functional Status Scale (FSS). This scale looks at five areas of function of your child while they are in the ICU. While your child is in the ICU, they will receive standard, routine physiotherapy treatment until discharge. We will then re-assess your child on discharge from ICU and again at discharge from the hospital.

Once we have completed all the assessments, we will collate and compare the data to note any changes in development, function, and quality of life throughout the transplant process.

If any delays or difficulties are picked up during the screening and assessments, we will refer your child appropriately.

Our aim of this study is to highlight any areas of difficulty that children with chronic liver diseases may be experiencing and ultimately, to determine if there is a need for further pre-operative and/or post-operative therapeutic interventions to help improve the functional outcomes of liver transplant.

If you agree to participate in the study, we will provide a consent form for you to sign and a demographics sheet to complete. At any point, you may withdraw your child from the study.

Regardless of whether your child participates in the study, they will still receive routine ICU physiotherapy and will be screened as per the unit on any hospital admissions and receive developmental or chest physiotherapy as is necessary.

If you have any questions regarding the research and the process of the study, please do not hesitate to contact:

Kyara Reynhardt: kyarareynhardt@gmail.com
+27 79 693 5456.
Prof. Joanne Potterton: joanne.potterton@wits.ac.za
011 717 3702

This study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg (“Committee”). A principal function of this Committee is to safeguard the rights and dignity of all human participants who agree to participate in a research project and the integrity of the research.

If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Clement Penny, who may be

contacted on telephone number 011 717 2301, or by e-mail on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

Thank you for taking the time to read this letter.

Date: May 2022

Appendix b Consent Form

PARENT CONSENT SHEET

"Developmental and functional outcomes in children with chronic liver disease undergoing liver transplant: a longitudinal cohort study."

1. I have been given a Participant Information Sheet which explains the nature and processes involved in this study, which is attached hereto;
2. I was given time to read it, or had it read to me, in the language I best understand;
3. I was given time to ask any questions I wanted to and found any answers given to me to be reasonable and satisfactory;
4. I believe I fully understand why the study is being conducted and what the intended outcomes will be;
5. I understand that there will be no immediate benefit to me, should I agree to participate, nor will I receive any payment; conversely, participation will not cost me anything but my time;
6. I understand that, even if I initially consent to take part in the study, I may subsequently withdraw at any time and would not be required to give any reasons; if that happened, any data collected about me for the purposes of the study would immediately be destroyed, unless I give consent for it to be retained
7. I have been given a range of contact details, listed below. If I require further information or become concerned about any aspect of this study, I am free to speak to any of these contacts.

Name of Participant: _____

Date: _____

Place: _____

Email: _____

Telephone: _____

Signature or mark _____

Witnessed by:

Name of Witness: _____

Signature: _____

Date: _____

Contact details:

Kyara Reynhardt: kyarareynhardt@gmail.com

Prof. Joanne Potterton: joanne.potterton@wits.ac.za

HREC Chairperson: Prof Clement Penny: on Clement.Penny@wits.ac.za or 011 717 2301

HREC Secretariat: Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za or 011 717 2700/1234

Appendix c Functional Status Score

Table 1

FSS Domains of Functioning in the Functional Status Scale (FSS)

	1	2	3	4	5
	NORMAL	**MILD DYSFUNCTION**	**MODERATE DYSFUNCTION**	**SEVERE DYSFUNCTION**	**VERY SEVERE DYSFUNCTION**
MENTAL STATUS	Normal sleep/wake; appropriate responsivity	Sleepy but arousable to noise/touch/movement and/or periods of social nonresponsivity	lethargic and/or irritable	Minimal arousal to stimulus (stupor)	Unresponsive and/or Coma and/or Vegetative
SENSORY	Intact hearing and vision and responsive to touch	Suspected hearing or Suspected vision loss.	Not reactive to auditory stimuli or Not reactive to visional stimuli	Not reactive to auditory stimuli and Not reactive to visional stimuli	Abnormal response to pain or touch
COMMUNICATION	Appropriate non-crying vocalizations, interactive facial expressiveness, or gestures	Diminished Vocalization Diminished Facial Expression and/or social responsiveness	Absence of attention getting behavior	No demonstration of discomfort	Absence of communication
MOTOR FUNCTION	Coordinated body movements and Normal muscle control and Awareness of action and why it's being done	1 limb functionally impaired	2 or more limbs functionally impaired	Poor head control	Diffuse Spasticity, Paralysis, Decerebrate/Decorticate Posturing
FEEDING	All food taken by mouth with age appropriate help	NPO or need for age-inappropriate help with feeding	Oral and tube feedings	Parenteral Nutrition with oral or tube feedings	All parenteral nutrition
RESPIRATORY	Room air and no artificial support or aids	Oxygen and/or Suctioning	Tracheostomy	CPAP for all or part of the day and/or Mechanical ventilator support for part of the day	Mechanical ventilatory support for all of the day and night

Appendix d Ethical Clearance Certificate WDGMC

Wits University
Donald Gordon
Medical Centre

MEDICLINIC

Date: 1st June 2022

Attention:
The Chairperson
Human Research Ethics Committee (Medical), FHS, University of the Witwatersrand

Re: "Developmental and functional outcomes in children with chronic liver disease undergoing liver transplant: a longitudinal cohort study."
Investigators: Professor Joanne Potterton (supervisor) and Ms Kyara Reynhardt (MSc Physiotherapy candidate)

In my capacity as the Interim Director of the Transplant Unit at Wits Donald Gordon Medical Centre (WDGMC) and as the CEO of WDGMC, I hereby grant permission to Ms Kyara Reynhardt for the following:
(i) to include WDGMC as a research site for MSc degree
(ii) to access the Transplant Unit for clinical information on children undergoing liver transplant procedures at WDGMC. This includes access to clinical transplant work up files housed in the Transplant Unit and access to the HREC (Medical) approved clinical research database on REDCap (M190749) titled: "WDGMC Paediatric Liver Transplant Research Database."

Please be aware that no data collection will commence until an amended Clearance Certificate that approves WDGMC as a study site has been obtained from the Wits Human Research Ethics Committee (Medical).
Please submit the final HREC approval to Dr June Fabian (june.fabian@mweb.co.za) from WDGMC Research.

Yours faithfully,

Dr Sue TagerCEO, Interim Director of the Transplant Unit, Wits Donald Gordon Medical Centre
Tel: (+27) 011 356 6302; Mobile: 082 457 7134; Email: sue.tager@mediclinic.co.za

Appendix e Ethical Clearance Certificate HREC

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO: Professor J Potterton and Ms K Reynhardt
School of Therapeutic Sciences
Department of Physiotherapy
Medical School
University

E-mail: kyarareynhardt@gmail.com

CC: Supervisor: Professor J Potterton
<Joanne.Potterton@wits.ac.za>
and <HREC-Medical Research Office@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2022/10/25

REF: R14/49

PROTOCOL NO: **M220849** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Developmental and functional outcomes in children with chronic liver disease undergoing liver transplant: a longitudinal cohort study*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2003/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Professor J Potterton and Ms K Reynhardt

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220849

NAME: (Principal Investigator)	Professor J Potterton and Ms K Reynhardt
DEPARTMENT:	School of Therapeutic Sciences Department of Physiotherapy Medical School University
PROJECT TITLE:	*Developmental and functional outcomes in children with chronic liver disease undergoing liver transplant: a longitudinal cohort study*
DATE CONSIDERED:	2022/08/26
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Professor J Potterton
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/10/25

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

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 submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **August** and therefore reports and re-certification will be due in the month of **August** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator Date

Appendix f Turnitin Report

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Final Draft Dissertation By Kyara Reynhardt

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

DEPARTMENT OF PHYSIOTHERAPY

25 March 2024

To whom it may concern

Turnitin report Kyara Reynhardt

I have checked Ms Reynhardt's Turnitin report which has a total of 15%. I am satisfied that the reason for this is the fact that the system repeatedly identified common medical terminology as plagiarism eg 'developmental delay', 'chronic liver disease' etc. No single source was over 1%.

Kind regards
Prof Joanne Potterton.

Prof Joanne Potterton
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Physiotherapy Department

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27 August 2024

Postgraduate Committee
Faculty of Health Sciences
University of the Witwatersrand

Dear Prof Maria Papathanasopoulos

Re: Corrections to MSc Physiotherapy following examination:
Candidate: Kyara Reynhardt

Title of the study: Developmental and functional outcomes in children with chronic liver disease undergoing liver transplant: a longitudinal cohort study

I am satisfied with the student's responses to the examiners' comments.

Thank you.

Kind regards

Prof Veronica Ntsiea
Head of Physiotherapy Department
School of Therapeutic Sciences
Faculty of Health Sciences