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Ishika Mukherjee April 10, 2023

Understanding the impact of ECMO on long-term cognitive and physical functioning amongst Single Ventricle patients who underwent Stage 1 Palliation.

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Abstract

Understanding the impact of ECMO on long-term cognitive and physical functioning

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By Ishika Mukherjee

Background: Univentricular patients are at increased risk of mortality. Of these, patients who undergo extracorporeal membrane oxygenation are at higher risk of neurological complications. We aim to describe the short-term outcomes and long-term behavioral outcomes of univentricular patients that required ECMO in the immediate postoperative period after stage I palliation.

Methods: Single-center retrospective study with a prospective limb at an academic quaternary children's hospital. All patients who underwent stage I palliation between January/2010 – December/2017 were included and stratified into ECMO and non-ECMO groups. Patient characteristics and Functional Status Scores were collected. BRIEF-II assessment was performed for the enrolled patients. Analysis was performed using appropriate statistics with a significance level set at $p = 0.05$.

Results: in the study period, we had a cohort of 200 patients. Among those, 50 (25 %) required ECMO postoperatively. Of those, 34% survived to discharge, and 8 (47%, $p < 0.001$) had neurological complications. Among the enrolled cohort, ECMO patients had prolonged hospital length of stay (57 [49; 79.2] $p=0.05$), prolonged CICU length of stay (42 [23.8;49.2] $p<0.05$), and neurological complications 62.5% $p < 0.001$ when compared to non-ECMO patients. 25 % of ECMO patients had unfavorable outcomes based on FSS.
There is an increase in T scores in Global Executive Functioning, Emotional regulation, and Behavioral regulation among the ECMO group ($p < 0.05$).

Conclusion: Univentricular patients who require ECMO postoperatively are more likely to have challenges in executive functioning, emotional regulation, behavioral control, behavioral awareness, and behavioral tendencies when compared to non-ECMO patients.

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Tables and Figures

Introduction

Single ventricle heart disease (SVHD) is a detrimental congenital heart defect where commonly the left side of the heart is underdeveloped. Children who are diagnosed with SVHD undergo multiple open-heart surgeries. Surgeries for SVHD involve staged palliation, which is three-step staged palliation, or the child would have to go through a heart transplant. Staged palliation is viewed as a successful and significant accomplishment of congenital heart surgery [1]. Staged palliations include Stage I palliation, also known as the Norwood procedure; Stage II palliation, also known as the Glenn procedure; and Stage III palliation, known as the Fontan procedure. These enable children to establish well-functioning pulmonary and systemic circulation through the function of a single ventricle. Frequent medical complications are often seen because of staged palliation, such as prolonged intensive care [2], nutritional problems [3], neurodevelopmental delays, and impaired neurological development, particularly in language [4]. As a result, children who go through Fontan surgery, which is the third and last surgery to improve blood flow from the lower extremities up to the lungs, experience difficulty in areas of cognition which have downstream effects on attention, executive functioning, and psychosocial development.

This puts them at an increased risk for anxiety disorders and depression and developing mental health morbidities [5]. Neonates with congenital heart disease tend to have brain abnormalities, including white matter trauma before surgery [6]. Additionally, congenital heart disease involves risk for several developmental challenges and other critical health issues, including neurodevelopmental and cognitive delays, feeding and respiratory problems, and sleep issues [7].

Over the years, extracorporeal membrane oxygenation (ECMO) has been used for patients with cardiorespiratory failure [7]. More recently, the use of ECMO has expanded to include rescue therapy for refractory cardiac arrest, termed E-CPR, with increasing evidence that E-CPR can save lives. The first use of ECMO was performed on a neonate; it was successful on the patient and thus was implemented amongst other neonatal patient populations [8]. ECMO can reduce the mortality of neonates as opposed to the use of conventional mechanical ventilation [9] [10].

While ECMO and ECPR have become widely accepted as advanced therapies, they are still associated with significant morbidity and mortality. A study conducted by Hervey-Jumper et al. focused on a pediatric and neonate population on ECMO from 1990 to 2009 and found that intracranial hemorrhage occurred in 7.4%, cerebral infarction in 5.7%, and clinical seizures in 8.4% of all patients [11]. In particular, the incidence of neurological complications in neonates and children on ECMO is between 9.9% and 17.3% [12,13,14,15,16]. When looking at gestational age, neonates under 34 weeks who require ECMO have high rates of intracranial hemorrhage [17,18].

Furthermore, recent data from the Extracorporeal Life Support Organization (ELSO) registry showed that almost 20% of all ECMO patients have some form of neurological complication. Neuroimaging of these patients demonstrated abnormalities in 30–50% of cases [17, 18, 19], and up to 60% of cardiac ECMO patients who survived have moderate to severe neurological impairment [20]. These complications, including intracranial hemorrhage and ischemia, are major causes of death and long-term disability in ECMO patients. Following an acute neurologic injury (ANI) on ECMO, only 36% of children survive to hospital discharge.

Analyzing long-term neuro-developmental effects on neonates who have undergone ECMO support has shown forms of neurological impairment or disability in 20% -50% of surviving

neonates [21,22,23]. Little data exists to indicate that a significant percentage of ECMO children who survive to discharge go on to suffer from long-term disability, deficits, and cognitive delay [24,25].

When trying to understand the long-term outcomes of ECMO utilization in neonates, infants with seizures were found to have lower IQs at preschool age than those without seizures [26]. Infants that survived ECMO had verbal, spatial, and memory problems and attention deficits. In addition, prolonged ECMO support in neonate survivors was associated with reduced quality of life and behavior functioning [27]. 5-20 % of single ventricle patients following stage I palliation required ECMO in the immediate postoperative period [28]. However, the mortality of patients with HLHS who received ECMO support after stage I palliation was high [29].

We don't have enough data on long-term neurological and neurodevelopmental outcomes of ECMO utilization on neonates and infants with SVHD after stage I palliation. Looking at their long-term outcomes requires time and appropriate comparison to communities to account for the severity of illness and social factors [30,31].

Acute severe neurologic complications are more prevalent in neonates and children than adults. Schiller et al. described that among patients who required ECMO as neonates, motor function deficits were accounted for until school age, and many preschool children experience problems with their working speed, spatial ability tasks, and memory. In addition, outcomes from this study showed that children who survived neonatal treatment with ECMO tackle neurodevelopmental problems at school age [32]. Therefore, the long-term outcomes of ECMO support on development, school performance, and quality of life are not outlined and require further research [33].

Thus, a long-term follow-up of these children is yet to be researched to identify neuro-

developmental problems earlier in age to develop appropriate resources.

This study aims to assess the short and intermediate-term neurodevelopmental outcomes and behavioral and developmental functioning of single ventricle patients who survived ECMO after stage I palliation.

Aims:

Aim 1) Describe outcomes of univentricular patients that required ECMO in the immediate postoperative period after the Norwood procedure. This includes demographics, patient characteristics, cardiac diagnosis, complications, neurological complications, hospital length of stay, and total intensive care unit stay length.

Aim 2) Describe the outcomes of the Behavior Rating Inventory of Executive Function (BRIEF-II) assessment of univentricular patients who survived to hospital discharge post-stage I palliation among the ECMO vs. non-ECMO patients with sub-analysis based on their neurological complications recorded in the form of neuroimaging and EEG.

Aim 3) Comparing FSS at the time of discharge with the Behavior Rating Inventory of Executive Function (BRIEF-II) at ages five years of age and older to assess the long-term functional status of patients after discharge.

Subject group:

Patients diagnosed with single ventricle physiology who underwent Norwood procedure for stage 1 palliation from January 1st, 2010 – December 31st, 2017 (procedure diagnosis: Norwood procedure with either m-BTT shunt or Sano shunt (RV-PA conduit)).

Methods

Data collection:

This single-center retrospective cohort study included all patients with univentricular physiology who underwent a Stage I palliation between January 1st, 2010, and December 31st, 2017, at Children's Healthcare of Atlanta (CHOA), a free-standing, university-affiliated quaternary children's hospital. An internal surgical database was queried, and eligible surgical encounters were identified. There is a prospective limb of this study in the form of the BRIEF II questionnaire that was conducted. The study was approved by the Children's Healthcare of Atlanta Institutional Review Board (IRB# 00001631). Informed consent was waived.

With these parameters, the total patient number in our cohort came to (n=200). Moreover, we then identified which patients belonged to the ECMO population (n=50) or the non-ECMO population (n=150).

We collected demographic information, patient characteristics, and clinical and laboratory data on patients diagnosed with single ventricle physiology who required the Norwood procedure. We used EPIC, CHOA's electronic medical records system, to obtain recorded clinical and biological features. These features entailed birth weight, gestational age, gender, genetic syndromes, chromosomal structure abnormalities, ECMO usage or not, and neurological complications at discharge. Neurological complications will be categorized into composite neurological complications and sub-neurological types. Furthermore, we also looked at the overall length of hospital stay for each patient and the length of stay in the cardiac intensive cardiac unit (CICU).

Upon identifying our entire cohort, we assessed patients' survival to discharge from hospital admission (after completing the Norwood procedure). Then we identified the patients who are

still alive and can have their short-term functional status compared to their current long-term functional and cognitive status. The second cohort was identified as the patients who agreed to participate in the Behavioral Rating Inventory of Executive Function-II (BRIEF-II) assessment, which is 38 patients. For the entire cohort and second cohort, we divided both the ECMO group and the non-ECMO group into subcategories of whether patients in the group had suffered neurological complications; this would serve as a part of our analysis when comparing each patient's functional status at discharge.

Functional Status Scale (FSS)

We divided our patient group into four groups (ECMO patients who had neurological complications during hospitalization and those who didn't, and non-ECMO patients who had neurological complications during hospitalization and those who didn't) based on who survived to discharge, excluding those who did not make it to discharge. Furthermore, we excluded the patients who are currently deceased and didn't participate in the BRIEF-II assessment.

We used the Function Status Scale (FFS), a tool used to assess functional status in children from full-term newborns to adolescents, enabling us to evaluate Biological, Sensory, and Motor Functions in infants. [37]. FSS comprises 6 domains: Mental Status, Sensory Function, Communication, Motor functioning, Feeding, and Respiratory Status. Each domain receives a score of 1 (normal), 2 (mild dysfunction), 3 (moderate dysfunction), 4 (severe dysfunction), or 5 (very severe dysfunction).

Final scores range from 6 to 30. The higher the score, the more dysfunction. When children are admitted, they have a baseline score of 6, indicating that they are stable [38]. However, comparing their score from admission to discharge is important. We used Palumbo et al.'s

definition of new morbidity as an increase in three or more on a patient's FSS from ICU admission to discharge, which is indicative of a critical deterioration in a patient's functional status and a change in the patient's FSS score of 5 or more is known to correlate with unfavorable outcome [39].

This enables us to compare short-term effects at discharge and correlate them with their long-term behavioral outcomes in school among patients who are currently alive.

FSS Domains:

Mental status: In reference to an infant's sleep quality, normal (score of 1) would involve being in a restful state without any agitation. When the infant is awake, it acknowledges its awareness and state and is responsive to itself and the environment.

Sensory Function: Normally, infants would have intact hearing through the movement of their facial features toward sensations or sounds in the environment. This would involve their turning gaze to focus on an individual or object within their visual field.

Communication: To be scored within the normal range, the infant must use sound gestures and non-verbal communication to draw attention and facial expressions and words to convey demands.

Motor functioning: This domain involves examining an infant's movements with muscle control. For example, an infant can grab a stuffed animal or sucks its thumb. The infant should be aware of its own actions.

Feeding: To be categorized in the normal domain, all the food taken by the infant is guided with age-appropriate help.

Respiratory status: Normally, the infant should be breathing room air without artificial help

(suctioning, oxygen, or mechanical support).

Summary of score ranking breakdown of each domain on the Functional status scale (FSS)

	1	2	3	4	5
	NORMAL	MILD DYSFUNCTION	MODERATE DYSFUNCTION	SEVERE DYSFUNCTION	VERY SEVERE DYSFUNCTION
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
MOTOR FUNCTIONING	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
COMMUNICATION	Appropriate non-crying vocalization, interactive facial expression, gestures	Decreased Vocalization Decreased Facial Expression and/or social responsiveness	Lack of attention getting behavior	no demonstration of discomfort	Absence of communication
MENTAL STATUS	Normal sleep/wake; appropriate responsivity	Sleepy but arousable to noise/touch/movement and/or periods of social non responsivity	lethargic and/or irritable	Minimal arousal to stimulus (stupor)	Unresponsive and/or Coma and/or Vegetative
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

Behavioral Rating Inventory of Executive Function (BRIEF-II)

Upon obtaining our cohort, who survived discharge and are currently alive, to evaluate long-term behavioral outcomes, we conducted an assessment using the Behavioral Rating Inventory of Executive Function (BRIEF-II). BRIEF-II is an assessment of impairments of executive function [40]. BRIEF-II is a 63-item questionnaire that can be conducted on parents of children with critical illnesses to estimate cognitive functioning. It can be done in an online assessment platform or through interviews. We contacted the patient's parents through a 10–20-minute phone interview. These interviews informed us about the long-term impacts on daily executive function on children and the linked features of ADHD.

Upon administrating the BRIEF-II parent questionnaire, they responded with either (N=Never, S=Sometimes, or O=Often). The BRIEF-II parent ratings of the executive functions of their child are good predictors of a child's functioning in many domains, including the academic, social, behavioral, and emotional domains.

As part of the BRIEF-II questionnaire, it is broken down into two sub-analyses: The 'Clinical Scales' and the 'Indexes.' The Clinical Scales measure the extent to which the respondent reports problems with different types of behavior related to the seven domains of executive functioning (Inhibit, Working Memory, Shift, Plan/Organize, Task-monitor, Self-Monitor, and Emotional Control).

As part of the Indexes, it involved four domains: Behavior Regulation, Emotion Regulation, Cognitive Regulation Indexes, and the Global Executive Composite index. These serve as summary indicators of composite clinical scale behaviors, which fall into a category index.

Indexes:

Behavior Regulation (BRI)

The Behavior Regulation Index (BRI) incorporates a child's ability to regulate and monitor their behavior effectively. It is composed of the Inhibit and Self-Monitor clinical scales. As defined by BRIEF-II, age-appropriate behavior regulation is likely to be a precursor to appropriate cognitive regulation. It allows for cognitive regulatory processes to guide active problem-solving skills and overall supports self-regulation.

Emotion Regulation (ERI)

The Emotion Regulation Index (ERI) demonstrates a child's ability to regulate their emotional responses and to adjust to changes in the environment, requests, and people. It is composed of the Shift and Emotional Control clinical scales. As defined by BRIEF-II, age-appropriate emotion regulation and flexibility are precursors to effective cognitive regulation.

Cognitive Regulation Indexes (CRI)

The Cognitive Regulation Index (CRI) demonstrates a child's ability to control and re-direct their cognitive processes and to problem-solve effectively. It comprises the Working Memory, Plan/Organize, Task-Monitor, and Clinical scales and correlates with the ability to actively problem solve in various contexts and complete tasks such as schoolwork as defined by BRIEF-

II.

Global Executive Composite Index (GEC)

The Global Executive Composite (GEC) is an overarching summary score that incorporates all the BRIEF2 clinical scales together. Although reviewing the BRI, ERI, CRI, and individual scale scores is strongly recommended for all BRIEF2 profiles, the GEC can serve as a summary measure of a child's overall cognitive and executive functioning.

Clinical Scales

Inhibit

The Inhibit scale assesses inhibitory control and impulsivity in a child. This can be defined as the ability to control impulses and for a child to stop their own behavior when asked or when they need to.

Self-Monitor

The Self-Monitor scale assesses the impact of a child’s behavior on other people and outcomes. It measures if a child is aware of the outcomes of their own behaviors or how their behavior impacts the behavior of other children and their expectations on the standard of behavior.

Shift

The Shift scale measures the ability of a child to transition from one activity or problem to another depending on the demand. This includes a child’s ability to make transitions, tolerate change, problem-solve, or alternate attention, and change focus from one task to another.

If a child has mild deficits, this may hinder their ability to be flexible, compromising the efficiency of problem-solving, and they may get stuck or focused on a topic or problem. Severe deficits would entail continuous behaviors and resistance to change.

Emotional Control

The Emotional Control scale assesses the impact of executive function problems on emotional expression and measures a child's ability to modulate or regulate their emotional responses.

Working Memory

The Working Memory scale measures representational memory. BRIEF-II defines this as 'the c, encode information, or generate goals, plans, and sequential steps to achieve goals.' Looking at a child's working memory is important when they are trying to multi-task or achieve tasks with multiple steps.

Plan/Organize

The Plan/Organize clinical scale assesses a child's ability to accomplish current and future-oriented tasks. The scale has two components: Plan and Organize. The Plan component captures the ability to anticipate future events, set goals, and develop sequential steps prior, to carrying out a task or activity. The Organize component is linked with the ability to rank information, memorize, and recall main ideas when learning or communicating information. Children with mild or severe difficulties in this area often give examples of poor memory or test-taking abilities.

Task-Monitor

The Task-Monitor scale measures task-oriented monitoring or checking of their work-oriented habits. This clinical scale captures whether a child tests their performance during or when completing a task to ensure the accuracy or completeness of a goal.

T-scores:

Upon completing the BRIEF-II questionnaire, responses are converted to raw scores aligned with a T-score. *T* scores are used to interpret the level of executive functioning. The *T* scores provide information about an individual's scores relative to respondents' scores in the standardization sample. Percentiles represent the percentage of children in the standardization sample with scores at or below the same value, which was already pre-determined against the standard distribution of the BRIEF-II assessment (*SD* = 10).

For all BRIEF-II clinical scales and indexes, *T* scores from 60 to 64 are considered mildly elevated, and *T* scores from 65 to 69 are considered potentially clinically elevated. *T* scores at or above 70 are considered clinically elevated. In interpreting the BRIEF-II, a summary of individual items within each scale can produce useful information for comprehending the explicit nature of the child's elevated score on any given clinical scale or index.

Therefore, for this cohort, we can use the BRIEF-II score to understand the long-term behavioral challenges of children with single ventricle physiology who required ECMO post-Norwood operation vs. patients who didn't require ECMO postoperatively, regardless of neurological outcomes.

Likelihood of ADHD

Children and adolescents with attention-deficit/hyperactivity disorder (ADHD) have complications with executive functions related to working memory, planning and organization, and inhibitory control. Studies have shown children and adolescents with ADHD have a signature BRIEF profile with elevations across most BRIEF scales and peaks on the Working Memory scale. [42,43] Thus, we can use the BRIEF2 Working Memory scale *T* score to predict the likelihood that a child will be diagnosed with ADHD.

Data analysis

Statistical Methods:

Using Sharpiro-Wilk tests, all continuous variables in the cohort were assessed for normal distributions. Means and standard deviations were reported for normally distributed data, and medians and IQRs were reported for non-normally distributed data. Categorical data were reported as counts and percentages. Chi-squared or Fisher and Mann-Whitney U or T-tests were used to examine significant changes among patients with and without ECMO and with and without neurological complications. T-score determination was obtained by converting questionnaire item scores to raw scale scores using the BRIEF-II Scoring Summary Table (Appendix A). Raw scores were converted to T scores by matching the raw score to its corresponding percentile in the normative table (Appendix B), giving us a corresponding T-score. T scores from 60 to 64 are considered mildly elevated, and those from 65 to 69 are considered potentially clinically elevated. T scores at or above 70 are considered clinically elevated. When comparing T scores, we established a cut point; any T score that fell below 60

was considered within a normal population, and a T score above 60 was considered in our abnormal population.

When establishing summary descriptions of FSS and T scores, we developed a composite T score, creating a mean of total clinical scales. For FSS score distribution, we separated summary descriptions by each domain. As well as used a total FSS score of 7 and above to distinguish between patients who had a normal FSS score (=6) or an elevated score (FSS > 6).

Results:

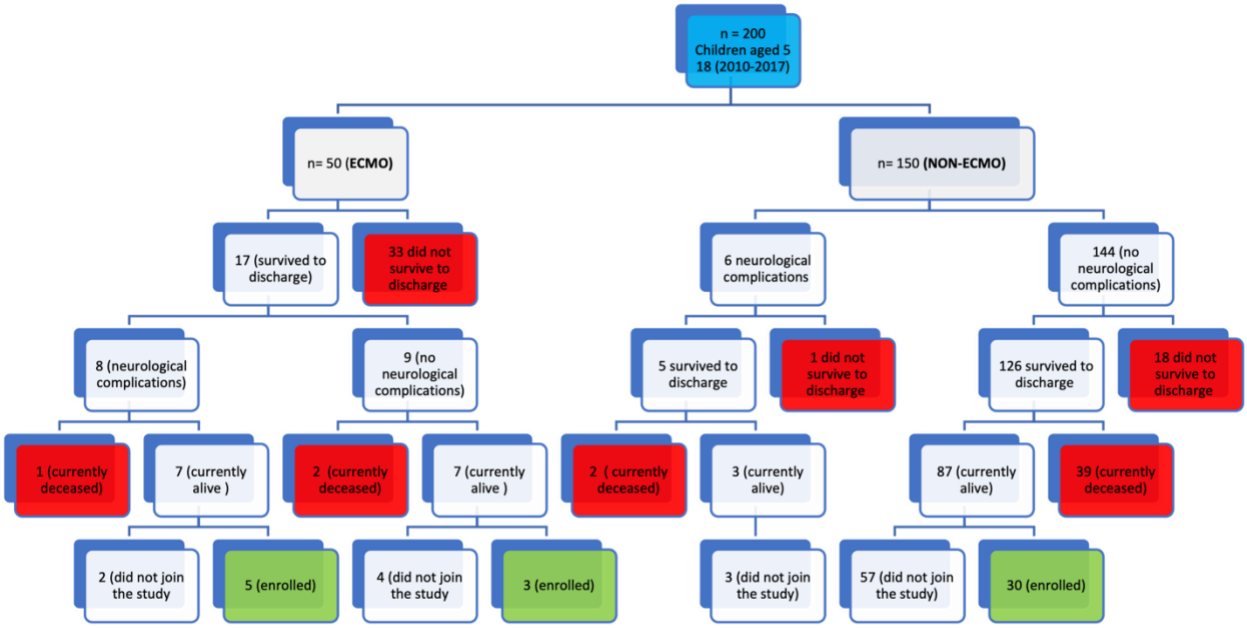
Study population:

A tree diagram of the entire cohort of this study is presented in (Figure 1). A total of 200 patients were identified as a part of our cohort. 150 patients were identified as non-ECMO patients (75.0%), and 50 were identified as ECMO patients (25%). Out of our ECMO population, 17 patients (34%) survived to discharge after completing Stage 1 palliation, and 33 patients did not make it to discharge (66%). Of those who survived to discharge in the ECMO group, 8 patients had neurological complications (47%). Out of those who are currently alive and presented with neurological complications and underwent ECMO, 5 patients were enrolled (71%).

For those who are presently alive, did not present with neurological complications, and underwent ECMO, 3 patients were enrolled (43%).

Under the non-ECMO population, 144 patients had no neurological complications (96%), and 6 patients had neurological complications (4%). Of those currently alive and had no neurological complications, 30 patients were enrolled (34%).

Figure 1: Tree diagram of the entire cohort who were diagnosed with single ventricle physiology who underwent Norwood procedure for stage 1 palliation between January 1st, 2010 and December 31st, 2017



Patient characteristics of the entire cohort are presented in (Table 1). There were 54 (36.0%) female and 96 (64.0%) male patients in the non-ECMO group. There were 17 (34.0%) female and 33 (66.0%) male patients in the ECMO group. The mean birth weight of patients in the non-ECMO group was 3.09 ± 0.49 vs. 3.04 ± 0.56 kg for the ECMO group. Neurological complications were significantly higher among patients who required ECMO postoperatively, 23 patients (46.6%) in the ECMO group, vs. 6 patients (4.0%) in the non-ECMO group with a *p*-value of < 0.001. The median ICU length of stay was higher among patients who required ECMO at 26.5 days vs.19.5 days for the non-ECMO group, with a *p*-value of 0.007. Mortality was higher among patients who required ECMO postoperatively 33 (66%) vs. patients who didn't require ECMO postoperatively 19 (12.7%), with a *p*-value of < 0.001. There was no

statistical difference in prematurity, chromosomal abnormalities, genetic syndromes, or cardiac diagnoses between the two groups.

Table 1: Patient Characteristics of the entire cohort stratified by ECMO and non-ECMO

Variables	**NON-ECMO (n = 150)**	**ECMO (n = 50)**	***p*-Value**
Gestational Age (weeks) (median [min;max])	38.0 [37.0;39.0]	38.0 [37.0;39.0]	0.571
Birth Weight (Kg) (mean)	3.09 ±0.49	3.04 ± 0.56	0.620
Gender			0.932
Female	54 (36.0%)	17 (34.0%)	
Male	96 (64.0%)	33 (66.0%)	
Preterm Birth (<36 week gestation) (n)			0.499
No	142 (94.7%)	45 (92.0%)	
Yes	8 (5.33%)	4 (8.00%)	
Genetic Syndrome			0.052
Cat-eye syndrome	1 (0.7%)	1 (2%)	
DiGeorge syndrome	5 (3.3%)	1 (2%)	
Fetal drug exposure	0 (0%)	2 (4%)	
Heterotaxy syndrome	8 (5.3%)	0	
Sickle cell Trait	2 (1.3%)	1(2%)	
Turner Syndrome	1(0.7%)	0	
CHARGE syndrome	1 (0.7 %)	0	
Familial CHD	5 (3.3 %)	0	
Other syndromic abnormalities	3 (2 %)	0	
Chromosomal abnormalities			0.595
22q11 deletion	5 (19.2%)	1 (50.0%)	
22q11 duplication	1 (3.85%)	0	
45X0	1 (3.85%)	0	
Other Chromosomal abnormality	17 (65.4%)	1 (50.0%)	
15q11	1 (3.85%)	0	
Trisomy 21	1 (3.85%)	0	
Neurological Complications			<0.001
No	144 (96.0%)	27 (54%)	
Yes	6 (4.0%)	23 (46.6%)	
Neurological Type			
Ischemic Stroke	1 (16.7%)	5 (21.7%)	
Seizure	2 (33.3%)	6 (26.1%)	
Hemorrhagic Stroke	3 (50.0%)	11 (47.8%)	
Intracranial hemorrhage	0	1 (4.35%)	
Hospital LOS (days) (median [min;max])	24.0[17.0;40.5]	34.64 [17.2;52.2]	0.2623
CICU LOS (days) (median [min;max])	19.5 [13.0;32.8]	26.5 [17.0;46.0]	0.007
Survived to Discharge			<0.001
No	19 (12.7%)	33 (66.0%)	

Yes	131 (87.3%)	17 (34.0%)	
Enrolled in study:			0.677
No	120 (80.0%)	42 (84.0%)	
Yes	30 (20.0%)	8 (16.0%)	
Primary cardiac diagnosis			0.509
Aortic stenosis/Aortic atresia	8 (5.33%)	3 (6.00%)	
HLHS	113 (75.3%)	36 (72.0%)	
Interrupted aortic arch + VSD	9 (6.00%)	2 (4.00%)	
Single Ventricle, Other	13 (8.67%)	4 (8.00%)	
TGA/ VSD	1 (0.67%)	0	
Tricuspid atresia /VSD	4 (2.67%)	5 (10.0%)	
VSD + Aortic arch hypoplasia	2 (1.33%)	0 (0%)	
HLHS VARIANT			0.748
MA/AA	42 (39.6%)	17(50.0%)	
MA/AS	6 (5.66%)	1 (2.94)	
MS/AA	36 (34.0%)	11 (32.4%)	
MS/AS	22 (20.0%)	5 (14.7%)	

Results depicted in n (percent), median [min and max]
HLHS: Hypoplastic Left Heart Syndrome; VSD: Ventricular Septal Defect; TGA: Transposition of the Great Arteries; MA: Mitral Atresia; MS: Mitral Stenosis; AA, Aortic Atresia; AS: Aortic Stenosis; CICU: Cardiac Intensive Care Unit; LOS: Length of Stay.

When limiting the cohort to our enrolled patients, (Table 2) represents patient characteristics stratified by ECMO status. There were 9 female patients (30.0%) and 21 male patients (70.0%) in the non-ECMO group. There were 3 female patients (37.50%) and 5 male patients (62.5%) in the ECMO group. The mean birth weight (Kg) of patients in the non-ECMO group was 3.00 ± 0.55 and 3.17 ± 0.55 for the ECMO group. Neurological complications were significantly higher among patients who required ECMO postoperatively, 5 patients (62.5%) in the ECMO group vs. none in the non-ECMO group, with a *p*-value of < 0.001. The median hospital length of stay was higher among patients who required ECMO at 57 days vs. 22.5 days for the non-ECMO group, with a *p*-value of 0.005. The median CICU length of stay was higher among patients who required ECMO at 42 days vs.18.5 days for the non-ECMO group, with a *p*-value of 0.0024. Mortality was higher among patients who required ECMO postoperatively 33 (66%) vs. patients who didn't require ECMO postoperatively 19 (12.7%), with a *p*-value of < 0.001. There was no statistical difference in prematurity, chromosomal abnormalities, or genetic syndromes between the two groups.

Table 2: Patient Characteristics of the enrolled cohort stratified by ECMO and non-ECMO

Variables	NON-ECMO (n = 30)	ECMO (n = 8)	*p*-Value
Gestational Age (weeks) (median [min;max])	39.0 [37.2;39.0]	38.5 [36.0;39.0]	0.232
Birth Weight (Kg) (mean)	3.00 ±0.55	3.17 ± 0.55	0.447
Gender			0.689
Female	9 (30.0%)	3 (37.5%)	
Male	21 (70.0%)	5 (62.5%)	
Preterm Birth (<36 weeks gestation)			0.499
No	29 (96.7%)	7 (87.5%)	
Yes	1 (3.33%)	1(12.5%)	
Chromosomal abnormalities			0.595
22q11 deletion	1 (20.0%)	0	
22q11 duplication	1 (20.0%)	0	
Other Chromosomal abnormality	3(60.0%)	1 (100%)	
Genetic Syndrome (n)			0.372
Cat-eye syndrome	c	1(50.0%)	
DiGeorge syndrome	1 (25.0%)	0	
Fetal drug exposure	0	1(50.0%)	
Heterotaxy syndrome	2 (50.0%)	0	
Neurological Complications			<0.001
No	30(100%)	3 (37.5%)	
Yes	0	5 (62.5%)	
Neurological Type			
Ischemic Stroke	0	2 (40.0%)	
Seizure	0	2 (40.0%)	
Hemorrhagic Stroke	0	1 (20.0%)	
Intracranial hemorrhage	0	1 (4.35%)	
Hospital LOS (days) (median [min;max])	22.5[17.8;39.0]	57.0 [49.0;79.2]	0.005
CICU LOS (days) (median [min;max])	18.5 [13.0;22.0]	42.0 [23.8;49.2]	0.024
Primary cardiac diagnosis			0.004
Aortic stenosis/Aortic atresia	1 (3.33%)	1 (12.5%)	
HLHS	24 (80.0%)	2 (25.0%)	
Interrupted aortic arch +VSD	3 (10.0%)	1 (12.5%)	
Single Ventricle Other	1 (3.33%)	1 (12.5%)	
TGA, VSD	1 (3.33%)	0 (0%)	
Tricuspid atresia/ VSD	0	3 (37.5%)	
HLHS VARIANT			0.043
MA/AA	9 (40.9%)	0	
MA/AS	0	1 (2.94)	
MS/AA	8 (36.4%)	0	
MS/AS	5(22.7%)	0	

Results depicted in n (percent), median [min and max]

HLHS: Hypoplastic Left Heart Syndrome; VSD: Ventricular Septal Defect; TGA: Transposition of the Great Arteries; MA: Mitral Atresia; MS: Mitral Stenosis; AA, Aortic Atresia; AS: Aortic Stenosis; CICU: Cardiac Intensive Care Unit; LOS: Length of Stay.

The FSS score difference between admission and discharge of the enrolled patient cohort is shown in (Table 3). We have 2 patients (25%) who have a change in FSS greater than 3 in the ECMO group vs. 3 patients (10.0%) in the non-ECMO group. 1 patient (3.33%) in the non-ECMO group had an FSS score change greater or equal to 5.

Table 3: Change in FSS at discharge among the enrolled cohort (ECMO and Non-ECMO) stratified by new morbidity and unfavorable outcome development.

Variables	New Morbidity (Change in FSS ≥ 3 points)			Unfavorable Outcome (Change in FSS ≥ 5 points)		
	Yes (n = 5)	No (n = 33)	*p*-value overall	Yes (n = 1)	No (n = 38)	*p*-value overall
ECMO GROUP	2(25.0%)	6 (75.0%)	0.279	0	8 (100%)	1.0
Non-ECMO GROUP	3 (10.0%)	27 (90.0%)		1 (3.33%)	29 (96.7%)	

FSS: Functional Status Scale; ECMO: Extracorporeal Membrane Oxygenation.

A summary of the Index scales of the BRIEF-II, along with mean and standard deviation values for the enrolled cohort stratified by ECMO status, is seen in (Table 4). ECMO patients had statistically significant T-scores in the GEC, ERI, and BRI index scales when compared to the non-ECMO group.

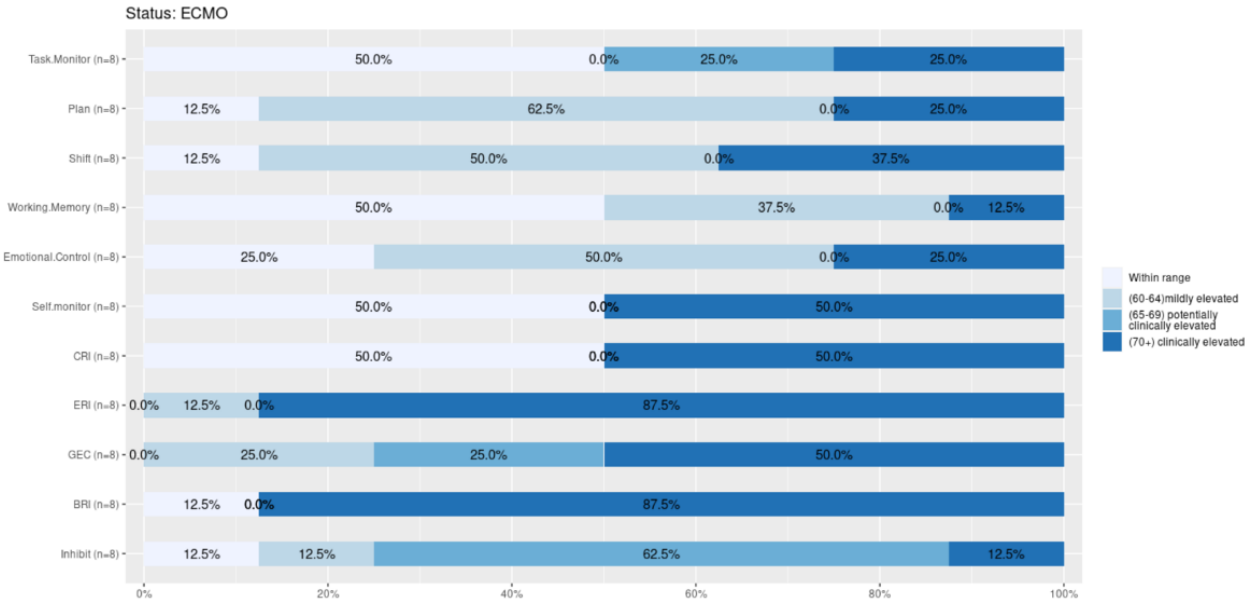
Table 4: Summary of Index scale indicators for BRIEF-II test administration among enrolled cohort stratified by ECMO status.

Variables	NON-ECMO (n = 30)	ECMO (n = 8)	*p*-Value
Global Executive Composite (GEC)	59.8 ± 10.8	68.9 ±5.11	0.002
Emotional Regulation (ERI)	60.3 ± 10.3	74.2 ± 10.9	0.008
Behavioral Regulation (BRI)	57.6 ± 11.9	66.0 + 3.25	0.002
Cognitive Regulation (CRI)	56.5±10.5	62.4± 9.81	0.167

ECMO: Extracorporeal Membrane Oxygenation.

The BRIEF-II questionnaire yielded T-scores for each clinical and index scale category; the results is shown for the ECMO group in (Figure 2). For the Inhibit clinical scale, 1 patient (12.5%) was within range, and 5 patients (62.5%) were potentially clinically elevated. For the BRI clinical scale, 1 patient (12.5%) was within range, and 7 patients (87.5%) were clinically elevated. For the GEC clinical scale, 2 patients (25%) were mildly elevated, and 4 patients (50%) were clinically elevated. For the ERI clinical scale, 1 patient (12.5%) was potentially clinically elevated, and 7 patients (87.5%) were clinically elevated. For the CRI clinical scale, 4 patients (50%) were within range, and 4 patients (50%) were clinically elevated. For the Self Monitor clinical scale, 4 patients (50%) were within range, and 4 patients (50%) were clinically elevated. For the Emotional Control clinical scale, 2 patients (25%) were within range, and 4 patients (50%) were mildly elevated. For the Working Memory clinical scale, 4 patients (50%) were within range, and 3 patients (37.5%) were mildly elevated. For the shift clinical scale, 1 patient (12.5%) was within range, and 3 patients (37.5%) were clinically elevated. For the plan clinical scale, 1 patient (12.5%) was within range, and 5 patients (62.5%) were mildly elevated. For the Task Monitor clinical scale, 4 patients (50%) were within range, and 2 patients (25%) were clinically elevated.

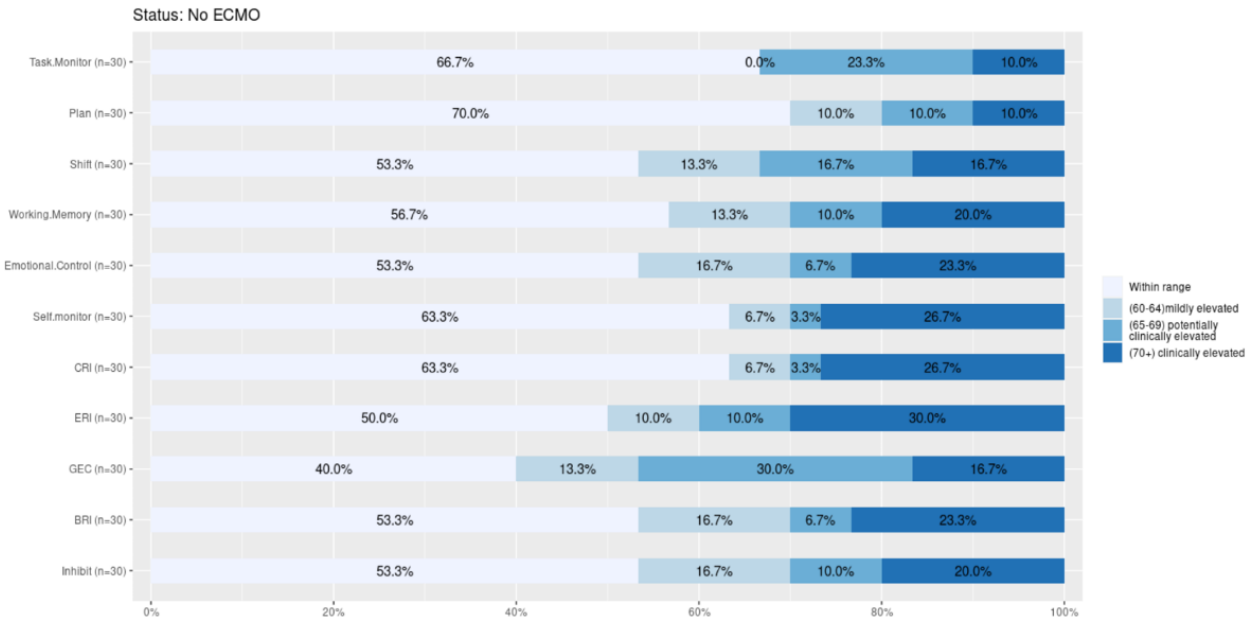
Figure 2: 11 Index and Clinical scale variables measured on the BRIEF-II questionnaire in the enrolled ECMO patients



The results of the BRIEF-II questionnaire yield T-scores for each clinical and index scale category is shown for the non-ECMO group in (Figure 3). For the Inhibit clinical scale, 16 patients (53.3%) were within range, and 6 patients (20%) were clinically elevated. For the BRI clinical scale, 16 patients (53.3%) were within range, and 7 patients (23.3%) were clinically elevated. For the GEC clinical scale, 12 patients (40%) were within range, and 9 patients (30%) were potentially clinically elevated. For the ERI clinical scale, 15 patients (50%) were within range and 9 patients (30%) were clinically elevated. For the CRI clinical scale, 19 patients (63.3%) were within range, and 8 patients (26.7%) were clinically elevated. For the Self Monitor clinical scale, 19 patients (63.3%) were within range, and 8 patients (26.7%) were clinically elevated. For the Emotional Control clinical scale, 16 patients (53.3%) were within range, and 7 patients (23.3%) were clinically elevated. For the Working Memory clinical scale, 17 patients (56.7%) were within range, and 6 patients (20%) were clinically elevated. For the Shift clinical

scale, 16 patients (53.3%) were within range, and 5 patients (16.7%) were clinically elevated. For the Plan clinical scale, 21 patients (70%) were within range, and 3 patients (10%) were clinically elevated. For the Task Monitor clinical scale, 20 patients (66.7%) were within range, and 7 patients (23.3%) were potentially clinically elevated.

Figure 3: <u>11 Index and Clinical scale variables measured on the BRIEF-II questionnaire for enrolled non-ECMO patients</u>



The likelihood of ADHD diagnosis compared between the enrolled ECMO and non-ECMO groups is shown in (Table 5). There were 7 patients (29.2%) in the ECMO group who had a positive likelihood of ADHD and presented symptoms in the BRIEF-II questionnaire. There were 17 patients (70.8%) in the non-ECMO group who had a positive likelihood diagnosis of ADHD and presented symptoms in the BRIEF-II questionnaire. Patients had 5.35 higher odds of the likelihood of ADHD when comparing ECMO and non-ECMO groups but didn't reach statistical significance *p*.ratio 0.129.

Table 5: Likelihood of ADHD diagnoses compared between ECMO and non-ECMO groups among enrolled patients.

Variables	Yes (n = 24)	No (n = 14)	*OR*	*p. ratio*	*p*-value overall
ECMO GROUP	7(29.2%)	1(7.14%)			0.216
Non-ECMO GROUP	17 (70.8%)	13 (92.9%)	5.35[0.58;49.1]	Ref.0.129	

ADHD: Attention Deficit Hyperactivity Disorder; ECMO: Extracorporeal Membrane Oxygenation.

Comparing the difference in T-scores of all variables between the ECMO patients who had neurological complications (ECMO (+) Neuro (+)) versus those who didn't (ECMO (+) Neuro (-))is summarized in (Table 6). There was no statistical difference in any of the 11 index and clinical scales among the two groups.

Table 6: Willcox test for (ECMO (+) Neuro (-) versus ECMO (+) Neuro (+) on BRIEF-II

Variables	ECMO (+) Neuro (-) (N = 3)	ECMO (+) Neuro (+) (N = 5)	*p*-Value
Task Monitor	56.0 ±17.0	61.6±13.3	0.654
Plan/Organize	67.0±8.72	63.8±9.42	0.648
Shift	71.3±15.4	69.0±14.6	0.842
Working Memory	54.0±8.19	60.2±11.9	0.418
Emotional Control	62.0 [60.5;70.5]	62.0[62.0;64.0]	1.000
Self-Monitor	63.0 [60.5;64.0]	63.0 [63.0;64.0]	0.878
CRI	60.3±11.7	63.6±9.76	0.707
ERI	77.7±11.9	72.2±11.1	0.554

GEC	68.7±6.66	69.0±4.85	0.944
BRI	68.0[67.0;68.5]	66[64;68.0]	0.219
Inhibit	68.7±1.53	63.8±5.36	0.115

ECMO: Extracorporeal Membrane Oxygenation; CRI: Control Regulation Index ; ERI: Emotional Regulation Index ; GEC: Global Executive Composite; BRI: Behavioral Regulation Index.

Assessing differences in T-scores between ECMO who had neurological complications (ECMO (+) Neuro (+)) versus non-ECMO who didn't have neurological complications (ECMO (-) Neuro (-)) is summarized in (Table 7). There was a statistically significant worsening in the T scores among the (ECMO (+) Neuro (+)) patients vs. ((ECMO (-) Neuro (-)) patients in the Self Monitor (62.2±2.95 vs. 55.2±11.2; *p*-value= 0.008), Global Executive Composite (71.0[68.0;72.0] vs. 63.5[53.0;68.0]; *p*-value= 0.04) and Behavioral Regulation Index (65.0±3.74 vs. 57.6±11.9; *p*-value= 0.014). There was no difference between the two groups in the Task Monitor, Plan/Organize, Shift, Working Memory, Emotional Control, Cognitive Regulation Index, Emotional Regulation Index, or Inhibit scales.

Table 7: Willcox test for (ECMO (-) Neuro (-) versus ECMO (+) Neuro (+) on BRIEF-II

Variables	**ECMO (-) Neuro (-) (N = 30)**	**ECMO (+) Neuro (+) (N = 5)**	***p*-Value**
Task Monitor	54.0 [44.0;66.0]	68.0[58.0;69.0]	0.247
Plan/Organize	54.9±9.82	63.8±9.42	0.104
Shift	60.1±9.75	69.0±14.6	0.251
Working Memory	58.2±11.9	60.2±11.9	0.744
Emotional Control	59.0±11.4	64.8±7.05	0.165
Self-Monitor	55.2±11.2	62.2±2.95	0.008
CRI	56.5±10.5	63.6±9.76	0.192

ERI	60.3±10.3	72.2±11.1	0.072
GEC	63.5[53.0;68.0]	71.0[68.0;72.0]	0.040
BRI	57.6±11.9	65.0±3.74	0.014
Inhibit	58.7±13.2	63.8±5.36	0.157

ECMO: Extracorporeal Membrane Oxygenation; CRI: Control Regulation Index; ERI: Emotional Regulation Index; GEC: Global Executive Composite; BRI: Behavioral Regulation Index.

Assessing differences in T-scores between ECMO and non-ECMO patients who didn't have neurological complications (ECMO (+) Neuro (-)) versus (ECMO (-) Neuro (-)) is summarized in (Table 8). There was a statistically significant worsening in the T scores among the (ECMO (+) Neuro (-)) patients vs. ((ECMO (-) Neuro (-)) patients in the Inhibit scale (68.7±1.53 vs. 58.7±13.2; *p*-value= 0.001), and Behavioral Regulation Index (67.7±1.53 vs. 57.6±11.9; *p*-value= < 0.001). There was no difference between the two groups in the Task Monitor, Plan/Organize, Shift, Working Memory, Emotional Control, Self-Monitor, Cognitive Regulation Index, Global Executive Composite, or Emotional Regulation Index.

Table 8: Willcox test for (ECMO (-) Neuro (-) versus ECMO (+) Neuro (-) on BRIEF-II

Variables	**ECMO (-) Neuro (-) (N = 30)**	**ECMO (+) Neuro (-) (N = 3)**	***p*-Value**
Task Monitor	54.0 [44.0;66.0]	56.0 [47.5;64.5]	0.900
Plan/Organize	54.9±9.82	67.0±8.72	0.125
Shift	60.1±9.75	71.3±15.4	0.332
Working Memory	58.2±11.9	54.0±8.19	0.477
Emotional Control	59.0±11.4	66.7±10.8	0.345
Self-Monitor	55.2±11.2	62.0±3.61	0.051
CRI	56.5±10.5	60.3±11.7	0.635
ERI	60.3±10.3	77.7±11.9	0.118
GEC	63.5[53.0;68.0]	67.0 [65.0;71.5]	0.233

BRI	57.6±11.9	67.7±1.53	<0.001
Inhibit	58.7±13.2	68.7±1.53	0.001

ECMO: Extracorporeal Membrane Oxygenation; CRI: Control Regulation Index; ERI: Emotional Regulation Index; GEC: Global Executive Composite; BRI: Behavioral Regulation Index.

To investigate whether there was a correlation between FSS and T scores in our patient population. We created a composite T score of all variables from the BRIEF-II survey and selected patients who have abnormal composite T scores, yielding a cohort of 26 patients who were stratified by their ECMO status into 18 patients in the non-ECMO group and 8 patients in the ECMO group.

A summary of the change in FSS at discharge within the cohort that has abnormal T scores stratified by ECMO and non-ECMO status is seen in (Table 9). All patients had an FSS score of 6 on admission, and a change of FSS score at the discharge of 1 or above was analyzed. A change in FSS score of 1 was noted in 1 patient (12.5%) in the ECMO group versus 0 patients in the non-ECMO group. A change in FSS score of 2 was seen in 5 patients (62.5%) in the ECMO group versus 17 patients (94.4%) in the non-ECMO group. A change in FSS score of 3 was seen in 2 patients (25%) in the ECMO group vs. 1 patient (5.56%) in the non-ECMO

Table 9: Summary of change in FSS scores among patients with abnormal T scores stratified by ECMO versus non-ECMO

Change in FSS at discharge	**ECMO (N = 8)**	**Non ECMO (N = 18)**	***p*-Value overall**
1	1(12.5%)	0	0.072
2	5 (62.5%)	17 (94.4%)	
3	2 (25.0%)	1 (5.56%)	

FSS: Functional Status Scale; ECMO: Extracorporeal Membrane Oxygenation.

To investigate whether there was a correlation between FSS and T scores in our patient population stratified by ECMO and non-ECMO, a summary was made to compare each domain of FSS amongst the patients with abnormal composite T-scores, as seen in (Table 10). For Feeding Function, there were 100% abnormal T scores in the non-ECMO group and 85.7% abnormal T scores in the ECMO group. For Respiratory function, there were 11.1% abnormal T score values in the non-ECMO group vs. 37.5 % abnormal T score values in the ECMO group.

Table 10: Summary of FSS domains compared between ECMO and non ECMO

Variables	**Non ECMO (N = 18)**	**ECMO (N = 8)**	***p*-Value overall**
Mental Status (normal)	18 (100%)	8(100%)	-
Sensory Function (normal)	18 (100%)	8(100%)	-
Communication (normal)	18 (100%)	8(100%)	-
Motor Functioning (normal)	18 (100%)	8(100%)	-
Feeding			0.308
Abnormal	18 (100%)	7 (85.7%)	
Normal	0	1 (14.3%)	
Respiratory			0.072
Abnormal	2 (11.1%)	3 (37.5%)	
Normal	16(88.9%)	5 (62.5%)	

FSS: Functional Status Scale; ECMO: Extracorporeal Membrane Oxygenation.

Discussion:

In this study of the total cohort of SVHD patients who underwent stage I palliation, only 34.0% of the patients who required ECMO postoperatively survived to hospital discharge compared to 87.3% of patients in the non-ECMO group. CICU and hospital length of stay were significantly prolonged in the ECMO group. 46.6 % of ECMO patients suffered neurological complications

compared to 4 % among non-ECMO patients. Running a Fisher's Exact test on neurological complication types yielded a significant difference between the two groups for ischemic stroke (5 (21.7%) vs. 1 (16.7%) (p <0.001)) ECMO patients versus non-ECMO, respectively.

When examining the cohort that was enrolled in the behavioral assessment (BRIEF-II), patients who required ECMO post-operatively vs. non-ECMO group had significantly prolonged hospital length of stay at a median of 57.0 days vs. a median of 22.5 days, as well as prolonged CICU length of stay 42 days [23.8;49.2] vs. 18.5 days [13.0;22.0]. 62.2 % of patients who required ECMO had neurological complications when compared to none among the non-ECMO patients. Although there are currently 3 patients who are alive within the non-ECMO group who were identified as having neurological complications during their hospitalization post stage I palliation, they did not agree to be enrolled in the study.

Changes in FSS at the time of discharge were only significant in the Respiratory Function domain amongst the ECMO group (see appendix). Of these patients, 25% developed new morbidity within the ECMO group compared to 10 % in the non-ECMO group; although it didn't reach statistical significance, it is likely due to the small sample size in the enrolled cohort. Comparing summary clinical indicator scales and indexes between non-ECMO and ECMO groups yielded values of statistical significance within GEC, BRI, and ERI. Elevated T scores within the Global Executive Composite scale demonstrate that there is a difference in overall executive functioning between ECMO and non-ECMO groups. The ECMO group, therefore, is likely to face challenges in cognitive processes that are required for the cognitive control of specific or overall behavior. Within the Emotional regulation index, patients in the ECMO group had more difficulties in their emotional regulation compared to the non-ECMO group. While for

the Behavioral Regulation index scale, the ECMO group is more likely to struggle to regulate and control their behavior effectively when compared to the non-ECMO group.

The ECMO group showed a significantly higher T-score in the Inhibit clinical scale than the non-ECMO group; this means that children within the ECMO group are more likely to struggle with the ability to control their impulses and to stop their own behavior when asked.

Furthermore, the ECMO group showed a significantly higher T-score in the Self-Monitor clinical scale than the non-ECMO group, concluding that children within the ECMO group are more likely to have challenges with how their behavior impacts the behavior of other individuals and their awareness of their own behavior in an environment.

Amongst the enrolled cohort, 63.2 % of patients had a positive likelihood of ADHD diagnosis. While stratifying the cohort based on their ECMO status, there was no statistical significance between the two groups, but they had 5.35 higher odds of the likelihood of ADHD.

When correlating abnormal composite T-scores with changes in discharge FSS amongst the enrolled cohort and stratifying them by their ECMO status, we found that 25 % of ECMO patients had an FSS score change of 3 compared to 5 % of non-ECMO patients. As previously described, a change of 3 or more in discharge FSS indicates an unfavorable outcome which in turn correlates with an abnormal T score.

Conclusion:

- From this study, we can conclude that ECMO patients had more neurological complications, longer hospital length of stay, longer CICU length of stay, and higher mortality when compared to non-ECMO patients.

- ECMO patients are more likely to have challenges in executive functioning, emotional regulation, and behavioral tendencies when compared to non-ECMO patients.
- ECMO patients are more likely to struggle with the ability to control their behavioral impulses, their own behavioral awareness, and how it impacts others.
- ECMO patients are more likely to have unfavorable outcomes.

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APPENDIX

Appendix A: Graph of FS~~F~~S patients with FSS > 3 VERUS clinical scale indexes