Impact of Maternal-Fetal Environment on Outcomes Following the Hybrid Procedure in the Single Ventricle Population

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Abstract

Introduction: Treatment of infants with hypoplastic left heart syndrome (HLHS) remains challenging, and those affected remain with significant risks for mortality and morbidity throughout their lifetimes. The maternal-fetal environment (MFE) has been shown to affect outcomes for infants with HLHS after the Norwood procedure. The hybrid procedure, comprised of both catheterization and surgical components, is a less invasive option for initial intervention compared to the Norwood procedure. It is unknown how the MFE impacts outcomes following the hybrid procedure.

Methods: This is a single-center, retrospective study of infants born with HLHS who underwent hybrid palliation from January 2009-August 2021. Predictor variables analyzed included fetal, maternal, and postnatal factors. The primary outcome was mortality prior to Stage II palliation.

Results: We studied a 144-subject cohort. There was a statistically significant difference in mortality prior to stage II palliation in infants with prematurity, small for gestational age, and aortic atresia subtype ($p<0.001$, $p=0.009$, and $p=0.008$, respectively). There was no difference in mortality associated with maternal diabetes, hypertension, obesity, smoking or illicit drug use, or advanced maternal age. State and national area deprivation index scores were associated with increased risk of mortality in the entire cohort, such that infants born in areas with higher deprivation had a higher incidence of mortality.

Conclusions: Several markers of an impaired MFE, including prematurity, small for gestational age, and higher deprivation index scores, are associated with mortality following hybrid palliation. Individual maternal comorbidities were not associated with higher mortality. The MFE may be a target for prenatal counseling and future interventions to improve pregnancy and neonatal outcomes in this population.

Introduction

The maternal-fetal environment (MFE) plays an important role in the health of the developing fetus. Impairments of this environment can contribute to significant morbidity and mortality in newborns [1–3]. This environment is impacted by numerous factors, including pre-existing or acquired health conditions in the mother, exposures throughout the pregnancy, as well as factors related to socioeconomic status, including insurance, access to healthcare, education level, and employment. Impaired MFE can lead to poor fetal growth and preterm birth [4, 5]. Thus, infant characteristics including small for gestational age (SGA) and prematurity may be postnatal markers of an impaired MFE.

Previous studies have analyzed the impact of the MFE on surgical outcomes as well as overall mortality for neonates with congenital heart disease (CHD). Among all infants undergoing surgical repair for CHD, an impaired MFE, defined by Gaynor et. al as the presence of gestational hypertension, pre-eclampsia, SGA, or preterm birth, was associated with longer post-operative length of stay and significantly lower survival at 36 months compared to infants exposed to a MFE without identified risk factors [6]. Another population-based study found poorer survival in those who were preterm, low birth weight, and in the most deprived areas [7].

The single ventricle population, including infants with hypoplastic left heart syndrome (HLHS) or HLHS variants, is a unique subset of patients with CHD who require surgical intervention within the first week of life. The Norwood procedure is the most common initial surgical palliation. The hybrid stage I (HS1) palliation is an alternative intervention that includes surgical placement of bilateral pulmonary artery bands, transcatheter atrial septostomy, and placement of a stent across the ductus arteriosus. Relative to the classic Norwood procedure, benefits to the HS1 palliation include a less invasive procedure in the neonatal period prior to maturation of the neonatal brain, shortened anesthesia exposure, avoidance of cardiopulmonary bypass and arch reconstruction, and less risk of end-organ injury including kidney injury [8]. Although often reserved at many institutions for smaller infants of younger gestational age or high-risk surgical candidates [9], the hybrid procedure is routinely the initial palliation of choice for HLHS at Nationwide Children's Hospital (NCH).

Stage I palliation, whether Norwood or hybrid, is associated with significant morbidity and mortality. The interstage period, the time between the first and second stages of palliation, is a particularly vulnerable period. The Single Ventricle Reconstruction Trial analyzed a large cohort of single ventricle patients who underwent Norwood palliation, and over half of the mortality in this population occurred with the stage I palliation, while interstage mortality accounted for another one-third of the deaths [10]. Impaired MFE, defined as maternal gestational hypertension, pre-eclampsia, gestational diabetes, and/or smoking during pregnancy, was associated with a significantly higher risk of death following the Norwood procedure [11]. Identified independent sociodemographic risk factors for interstage mortality following the Norwood procedure include teen mothers and single caregivers [12].

The impact of the MFE has not been applied the hybrid procedure. This study will investigate potential factors that may identify patients with higher risk for mortality following the hybrid procedure based on their MFE. We hypothesize that among patients with HLHS who undergo the hybrid procedure, there will be an increased risk for poor surgical outcomes in those with an impaired MFE.

Methods

We conducted a retrospective, observational cohort study at NCH for patients born between January 2009 and August 2021. Inclusion criterion was infants born with single ventricle CHD with a dominant right ventricle and aortic arch obstruction who underwent HS1 palliation at NCH with intention to treat for complete single ventricle palliation. Exclusion criteria included infants with single left ventricle, infants who underwent a subsequent two-ventricle repair or palliation without intention to treat, infants with incomplete records including those who underwent HS1 palliation at an outside institution or were lost to follow up, and infants with Trisomy 21. The primary outcome was mortality prior to stage II palliation. Data were obtained through the NCH electronic medical record in the infant's chart, which included prenatal, postnatal, and maternal data. Additional maternal records were obtained through a shared electronic medical record in the mother's chart when available. This study was approved by the Institutional Review Board at NCH.

The MFE was evaluated using fetal, maternal, and postnatal factors reflecting the fetal environment. Collected fetal variables included gender, gestational age, and diagnosis (anatomic subtype, restriction of the atrial septum, major genetic diagnosis, and presence of a prenatal diagnosis). Gestational age was used to identify premature infants, defined as those born prior to 37 weeks gestational age. Determination of anatomic subtype was defined by the presence of aortic atresia. Atrial septum restriction was defined by the need for urgent atrial septal intervention within the first 48 hours of life. Major genetic syndromes included in the study were Turner Syndrome, Jacobsen Syndrome, and Kabuki syndrome. There were no patients in our cohort with Trisomy 18 or CHARGE syndrome.

Maternal variables analyzed included maternal race, insurance type, nine-digit zip codes, and the presence of five maternal risk factors, including advanced maternal age (≥ 35 years old), smoking or illicit drug use, diabetes (gestational or pregestational), hypertension (gestational or pregestational), or obesity (body mass index ≥ 30kg/m^2). Maternal race was categorized as Caucasian or non-Caucasian. Insurance type was categorized as Medicaid or private insurance. The nine-digit zip code was used to generate state and national area deprivation index (ADI) scores using the Neighborhood Atlas, developed by the University of Wisconsin-Madison [13, 14]. Maternal risk factors were analyzed individually and as a composite, comparing the presence of any risk factors (one or more) to the absence of all risk factors. Smoking and illicit drug use were determined based on self-reported use at any time during the pregnancy.

Postnatal data that was collected included birth weight, APGAR scores, pre-procedural data (respiratory support prior to intervention, brain-natriuretic peptide (BNP) within 24 hours prior to surgery, first neonatal creatinine as a marker of maternal milieu, age at time of hybrid palliation), and data from the initial echocardiogram after birth (right ventricular function, tricuspid regurgitation). Birth weight was used to identify infants who were SGA, defined as a birth weight less than the tenth percentile for their gestational age. Respiratory support prior to hybrid palliation was defined as the need for intubation, non-invasive positive pressure, or high-flow nasal cannula pre-operatively. Echocardiograms were performed in accordance with guidelines from the American Society of Echocardiography. All echocardiograms were independently reviewed for assessment of RV function and tricuspid regurgitation.

Based on previous studies suggesting higher mortality in HLHS infants with aortic atresia [15], a separate analysis was performed on infants with this anatomic subtype. A separate analysis was also performed on a cumulative high-risk subgroup, which included infants with any of the following features: birth weight less than 2.5kg, moderate or severe tricuspid regurgitation or right ventricular dysfunction after birth, a major genetic diagnosis, or a restrictive atrial septum. Variables in these analyses were selected based on significance in the univariable analysis, and additional maternal risk factors were selected based on relatively high prevalence within our study.

Statistical Analyses

Continuous variables are presented as medians with interquartile range while categorical variables are presented as counts with proportion of the sample. Characteristics of infants who did and did not experience mortality were compared using Wilcoxon rank-sum tests for continuous variables or Fisher's exact tests for categorical variables. Similar comparisons were made for infants with and without aortic atresia subtype as well as infants meeting criteria for the cumulative high-risk subgroup. The relationship between the ADI and prematurity, SGA, and the presence of maternal risk factors was visualized using box plots. Logistic regression was used to estimate the adjusted effect of National ADI, aortic atresia subtype, and prematurity on mortality prior to stage II palliation. P values of < 0.05 were considered significant and all confidence intervals are 95% confidence intervals. All analysis was conducted in R version 4 [16, 17] and all graphs were made using ggplot2 [18].

Results

Between January 2009 and August 2021, there were 151 infants with HLHS who underwent the hybrid procedure. Seven were excluded – two secondary to a diagnosis of Trisomy 21, two due to hybrid palliation without intention to treat through the single ventricle pathway, two additional infants who underwent hybrid palliation at an outside institution, and one infant was lost to follow-up after transferring to another institution. The final cohort consisted of 144 infants who met inclusion criteria for our study.

Fetal and maternal demographics are listed in Table 1. The majority of infants had a prenatal diagnosis of HLHS (81%) and were born full term (88%). Among the 17 infants born prematurely, the median gestational age was 35 weeks (range 31–36 weeks). Median birth weight was 3.140kg. There were 17 infants with an absolute birth weight < 2.5kg and 23 infants (16%) in the final cohort were SGA. There were 28 infants in our study whose mothers resided from a state other than Ohio. 105 mothers (73%) had at least one of the five maternal risk factors. Only two mothers had late prenatal care with care starting in the third trimester.

Table 1
Demographic Data

	Total Cohort (N = 144)
Baby Gender	
Male	89 (62%)
Female	55 (38%)
Prenatal Diagnosis	116 (81%)
Premature	17 (12%)
Gestational Age (weeks)	39 (38, 39)
Birth Weight (grams)	3,140 (2,812, 3,554)
Small for Gestational Age	23 (16%)
Restrictive Atrial Septum	8 (5.6%)
Major Genetic Diagnosis	8 (5.6%)
Turner Syndrome	4 (2.8%)
Jacobsen Syndrome	1 (0.7%)
Kabuki Syndrome	3 (2.1%)
Medicaid	56 (39%)
Number Out of State	28 (19%)
Maternal Race	
Caucasian	116 (81%)
Non-Caucasian	27 (19%)
Maternal Age (years)	28 (23, 33)
Maternal Risk Factors	
Advanced Maternal Age	27 (19%)
Smoking/Drug Use	25 (19%)
Diabetes	12 (8.6%)
Hypertension	20 (14%)
Obesity	76 (55%)

N (%); Median (IQR)

	Total Cohort (N = 144)
Late Prenatal Care	2 (1.6%)
N (%); Median (IQR)	

Premature: <37 weeks gestational age

Small for Gestational Age: Birth weight <10th percentile for gestational age

Restrictive Atrial Septum: Urgent atrial septal intervention within first 48 hours of life

Advanced Maternal Age: ≥35 years old

Obesity: Body mass index ≥30kg/m^2

Table 2 shows the relationship of fetal, maternal, and postnatal factors with mortality. Considering fetal factors, prematurity and aortic atresia subtype ($p < 0.001$ and $p = 0.008$, respectively) were associated with increased mortality prior to stage II palliation. No mortality difference was observed in maternal race, insurance type, or maternal risk factors. Higher state and national ADI scores, reflective of more deprived neighborhoods, were also associated with mortality ($p = 0.028$ and $p = 0.019$, respectively). Across postnatal factors, increased mortality was observed among infants with lower birth weight and those meeting criteria for SGA ($p = 0.039$ and $p = 0.009$). The need for respiratory support prior to hybrid palliation was also significantly higher among non-survivors ($p = 0.049$), while measured cardiac indices (right ventricular dysfunction, tricuspid regurgitation on first postnatal echocardiogram) were not associated with mortality following the hybrid procedure.

Table 2
Risk Factors for Mortality

	Mortality, N = 30[1]	No Mortality, N = 114[1]	p-value[2]
FETAL FACTORS			
Baby Gender			0.3
Male	16 (53%)	73 (64%)	
Female	14 (47%)	41 (36%)	
Prenatal Diagnosis	22 (73%)	94 (82%)	0.3
Premature	10 (33%)	7 (6.1%)	**< 0.001**
Aortic Atresia Subtype	23 (77%)	56 (49%)	**0.008**
Restrictive Atrial Septum	2 (6.7%)	6 (5.3%)	0.7
Genetic Diagnosis			0.4
Turner Syndrome	2 (6.7%)	2 (1.8%)	
Jacobsen Syndrome	0 (0%)	1 (0.9%)	
Kabuki Syndrome	0 (0%)	3 (2.6%)	
MATERNAL FACTORS			
Maternal Race			0.6
Caucasian	23 (77%)	93 (82%)	
Non-Caucasian	7 (23%)	20 (18%)	
Medicaid	14 (48%)	42 (37%)	0.3
Maternal Risk Factors			
Advanced Maternal Age	6 (20%)	21 (18%)	0.8
Smoking/Drug Use	6 (21%)	19 (18%)	0.8
Diabetes	2 (7.1%)	10 (8.9%)	> 0.9
Hypertension	2 (6.9%)	18 (16%)	0.2
Obesity	17 (68%)	59 (52%)	0.2
Number of Maternal Risk Factors			0.4
0	6 (20%)	33 (29%)	

[1]N (%); Median (IQR); [2]Fisher's exact test; Wilcoxon rank sum test

	Mortality, N = 30[1]	No Mortality, N = 114[1]	p-value[2]
1+	24 (80%)	81 (71%)	
State Area Deprivation Index (Decile)	7.00 (4.00, 9.00)	4.50 (2.25, 7.00)	**0.028**
National Area Deprivation Index (Percentile)	78 (59, 91)	63 (47, 81)	**0.019**
POSTNATAL FACTORS			
Small for Gestational Age	10 (33%)	13 (12%)	**0.009**
Birth Weight (grams)	2,879 (2,346, 3,381)	3,161 (2,900, 3,559)	**0.039**
Abnormal APGAR (< 7)	7 (24%)	15 (14%)	0.3
Respiratory Support Prior to Hybrid	15 (50%)	33 (29%)	**0.049**
Right Ventricular Function After Birth			> 0.9
Normal or Mild Dysfunction	28(93%)	105 (92%)	
Moderate or Severe Dysfunction	2 (6.7%)	9 (7.9%)	
Tricuspid Regurgitation After Birth			> 0.9
Normal or Mild	27 (90%)	101 (89%)	
Moderate or Severe	3 (10%)	13 (11%)	
BNP Prior to Hybrid	2,191 (1,689, 3,362)	3,622 (2,084, 4,930)	0.11
1st Neonatal Creatinine	0.78 (0.72, 0.98)	0.76 (0.63, 0.86)	0.089
Day of Life at time of Hybrid	5.5 (3.0,7.0)	5.0 (3.2,7.0)	> 0.9
[1]N (%); Median (IQR); [2]Fisher's exact test; Wilcoxon rank sum test			

Premature: <37 weeks gestational age

Restrictive Atrial Septum: Urgent atrial septal intervention within first 48 hours of life

Advanced Maternal Age: ≥35 years old

Obesity: Body mass index ≥30kg/m^2

Small for Gestational Age: Birth weight <10^{th} percentile for gestational age

Respiratory Support Prior to Hybrid: intubation, non-invasive positive pressure, or high-flow nasal cannula

BNP: Brain-natriuretic peptide

Figure 1 analyzes state and national ADI scores, reported as deciles and percentiles, by prematurity status, SGA status, and the presence of maternal risk factors. The median state and national ADI score for premature infants were 7.0 and 79, compared to 5.0 and 64 in term infants. Similarly, SGA infants tended to have higher median state and national ADI scores (7.0 and 82, respectively) compared to infants who were not SGA (5.0 and 64, respectively). The median state ADI score for moms with one or more maternal risk factors was 5.0, compared to a score of 4.0 for moms with no maternal risk factors. The median national ADI score for moms with one or more maternal risk factors was 69, compared to a score of 56 for moms with no maternal risk factors.

Within the two high risk subgroups identified, there were 79 infants with aortic atresia anatomic subtype and 45 infants in the cumulative high-risk subgroup (Table 3). Among infants with aortic atresia, mortality was 29% (23/79). Mortality was associated with prematurity, SGA, and lower birth weight. While state and national ADI scores trended higher in infants with mortality, this did not reach statistical significance. Among the 45 infants in the cumulative high-risk subgroup, there were 17 infants with birth weight < 2.5kg, 8 infants with a major genetic diagnosis, 8 infants with a restrictive atrial septum, 16 infants with moderate or severe tricuspid regurgitation, and 11 infants with moderate or severe right ventricular dysfunction. Within this subgroup, mortality was 29% (13/45). Mortality was again associated with prematurity and lower absolute birth weight. Similar to the aortic atresia subgroup, state and national ADI scores trended higher in infants with mortality in this subgroup but did not reach statistical significance.

Table 3
Risk Factors for Mortality in the Aortic Atresia Subtype and Cumulative High-Risk Group

	Aortic Atresia Subtype (N = 79)			**Cumulative High-Risk Group (N = 45)**		
	Mortality (N = 23)	**No Mortality (N = 56)**	**p-value**	**Mortality (N = 13)**	**No Mortality (N = 32)**	**p-value**
Prematurity	9 (39%)	4 (7.1%)	**0.001**	8 (62%)	4 (12%)	**0.002**
SGA	8 (35%)	4 (7.1%)	**0.004**	7 (54%)	7 (23%)	0.074
Birth Weight (grams)	2770 (2282, 3359)	3162 (2880, 3568)	**0.021**	2230 (1908, 2500)	3298 (2627, 3,599)	**0.004**
Maternal Hypertension	2 (9.1%)	7 (13%)	> 0.9	0 (0%)	4 (13%)	0.3
Maternal Obesity	12 (67%)	33 (60%)	0.8	6 (60%)	13 (41%)	0.5
Number of Maternal Risk Factors			0.8			0.2
0	6 (26%)	13 (23%)		2 (15%)	12 (38%)	
1+	17(74%)	43 (77%)		11 (85%)	20 (62%)	
State Deprivation Index (Decile)	7.0 (3.5, 9.0)	4.5 (2.0, 7.0)	0.066	7.0 (3.0, 9.0)	5.0 (2.75, 7.0)	0.2
National Deprivation Index (Percentile)	78 (56, 89)	60 (45, 79)	0.081	84 (54, 92)	67 (46, 82)	0.064
Respiratory Support Prior to Hybrid	10 (43%)	12 (21%)	0.058	7 (54%)	14 (44%)	0.7

[1]N (%); Median (IQR); [2]Fisher's exact test; Wilcoxon rank sum test; Wilcoxon rank sum exact test

Cumulative High-Risk Group: infants with any of the following features- birth weight <2.5kg, moderate or severe tricuspid regurgitation or right ventricular dysfunction after birth, a major genetic diagnosis, or a restrictive atrial septum

Premature: <37 weeks gestational age

SGA: Small for Gestational Age (birth weight <10th percentile for gestational age)

Maternal Obesity: Body mass index ≥30kg/m^2

Respiratory Support Prior to Hybrid: intubation, non-invasive positive pressure, or high-flow nasal cannula

Table 4 shows the odds ratios (OR) and corresponding confidence intervals (CI) for the adjusted effects of certain MFE factors and mortality prior to stage II palliation. The selected MFE factors were national ADI score, aortic atresia subtype, and prematurity. The adjusted OR of mortality prior to stage II palliation for national ADI score was 1.024 (CI: 1.003, 1.047), such that for a 1% increase in national ADI score, the odds of mortality increased by 2.4%. The OR for aortic atresia subtype and prematurity were 3.218 (CI: 1.249, 9.196) and 5.914 (CI: 1.953, 18.948), respectively.

Table 4
Logistic Regression Modeling Odds of Mortality

	Adjusted OR of Mortality Prior to Comprehensive Stage II (CI)
National Deprivation Index	1.024 (1.003, 1.047)
Aortic Atresia Subtype	3.218 (1.249, 9.196)
Premature	5.941 (1.953, 18.948)
OR Odds Ratio; *CI* Confidence Interval	

Premature: <37 weeks gestational age

Discussion

Despite significant advances in surgical and medical management in CHD, surgical palliation for infants with single ventricle CHD remains associated with significant mortality [10, 19]. Several studies have shown an association between an impaired MFE and post-operative mortality in this population [6, 11, 12]. However, these studies have primarily or exclusively included infants who underwent Norwood palliation. Our study goal was to evaluate the impact of the MFE on mortality in a large cohort of infants who underwent hybrid palliation for single ventricle CHD.

Previous studies defined an impaired MFE by the presence of maternal gestational hypertension, preeclampsia, gestational diabetes, smoking during pregnancy, preterm birth, or SGA [6, 11]. Our study evaluated the impact of these maternal co-morbidities of impaired MFE, as well as several other fetal, maternal, and postnatal factors in order to more broadly evaluate and capture an impaired MFE, including socioeconomic factors. ADI assesses socioeconomic status as a measure that includes factors such as education, employment, housing quality, and income to identify disadvantaged neighborhoods.

Fetal factors that were associated with higher mortality in our population included prematurity and aortic atresia, consistent with previous studies [6, 7, 15]. There were few infants within our cohort with a restrictive atrial septum or a major genetic diagnosis, making it difficult to adequately assess the role of these factors in mortality. Lack of a prenatal diagnosis did not impact mortality. However, this does not take into consideration other important benefits of a prenatal diagnosis including improvement in parental and care team preparation and planning, increasing the potential for prevention of significant infant comorbidities. Markkanen et. al demonstrated that prenatal diagnosis of HLHS is associated with improved postnatal right ventricular function, reduced metabolic acidosis, and reduced end-organ dysfunction [20]. Similarly, in our study, significant right ventricular dysfunction was seen exclusively in infants with a postnatal diagnosis, all of whom improved once the diagnosis was made.

Within our health system as a free-standing children's hospital, linkage of maternal-fetal data can be difficult. Using the electronic medical record, including the infant and mother's charts, we were able to collect 97% of maternal data points. The presence of at least one maternal risk factor within our cohort was overwhelmingly high, present in 73% of mothers. This is clinically important and concerning for poor overall maternal state of health. Although these risk factors individually were not associated with higher mortality, mortality tended to be higher in the presence of any risk factor compared to infants of mothers with zero risk factors. These maternal risk factors were also related to ADI scores. Mothers with one or more risk factors had a higher median ADI score compared to mothers with zero risk factors. In these maternal-fetal dyads, worse pregnancy outcomes (prematurity and SGA) also had a trend toward higher median ADI scores when compared to their term and average weight for gestational age counterparts. This has been shown in other population health studies of pregnancy outcomes [21–23]. This suggests an important relationship between overall maternal health, the MFE, socioeconomic status, and pregnancy outcome metrics of gestational age and birthweight. The impact of these relationships is potentially magnified when the infant is born with critical CHD such as HLHS. Future use of ADI scores may aid in the development and targeting of pre-pregnancy and prenatal intervention programs to improve the MFE for the highest risk maternal-fetal dyads.

Among infants with aortic atresia and those identified as cumulative high-risk, prematurity and lower birth weight remained significantly associated with mortality. ADI scores trended towards higher but not to statistical significance in the aortic atresia or cumulative high-risk groups. These analyses may be under-powered with the smaller cohort sizes. Alternatively, the increased risks conveyed by the anatomic subtype and other high-risk features may outweigh the added risk from socioeconomic status.

The model for our multivariate analysis was created as an exploratory analysis using 3 significant MFE factors from the univariable analysis. When adjusted for aortic atresia and prematurity, the OR for national ADI score approaches 1. Given the significance of this factor in the univariable analysis, this suggests that national ADI score may not be as indicative of higher mortality risk once prematurity and aortic atresia are accounted for. It is also possible that ADI provides similar information on mortality risk as prematurity, as mothers in a more deprived area with a higher ADI score may be at risk for premature delivery. However, it is important to consider that this is a continuous variable and the OR is

multiplicative. A 1% increase in national ADI score increases odds of mortality by 2.4%, so a change of several percentiles can become very significant. This analysis also shows that in the context of our patient population, prematurity increases the odds for mortality more than aortic atresia anatomic subtype, when considering national ADI score, prematurity and aortic atresia as mortality risk indicators.

Limitations

This study is limited by its retrospective nature. As expected, there were changes in management over the course of this retrospective study that impacted mortality. There are also patients with incomplete data, particularly related to maternal risk factors and in patients with a postnatal diagnosis for whom maternal history or neonatal data were not fully available. In instances where the status of a risk factor was unknown, if the mother indicated they did not have any other risk factors, the mother was assumed to have no risk factors. Therefore, we may have under-reported the presence of maternal risk factors given limitations associated with unique mother and baby electronic medical record systems.

There is also potential referral bias, with nearly one in five patients within our cohort being from out of state. Although we have a relatively large cohort, particularly considering the rare use of hybrid palliation on a national level, our study is still limited by patient numbers and power. There are few patients within our study with certain features, such as genetic syndromes, a restrictive atrial septum, or maternal history of diabetes, making it challenging to assess the full impact of such features on outcomes. Furthermore, our study does not include patients with fetal demise or mortality prior to hybrid palliation who may be even higher risk patients with more features of an impaired MFE.

Additionally, in the logistic regression analysis, there may exist confounding factors that were not incorporated into the model. The results of the logistic regression, namely OR and corresponding confidence intervals, should be interpreted as such.

Conclusion

This represents the first study to explore the impact of MFE on outcomes following hybrid palliation for HLHS. We identified several markers of an impaired MFE, including prematurity, SGA, and lower birth weight, that are associated with mortality in HLHS following HS1 palliation. Notably, our study also identified the important role of socioeconomic disadvantage in mortality following hybrid palliation. Although specific maternal comorbidities were not individually associated with higher mortality, infants who experienced mortality were more likely to be born to mothers from a more deprived area, as reflected by higher state and national ADI scores. This should be an important consideration in prenatal counseling and can also serve as a possible target for future modifiable interventions at the pre-pregnancy, prenatal, and postnatal stages to improve outcomes in this patient population. Moving forward, comprehensive efforts to improve maternal health and the MFE, specifically to decrease the incidence of preterm birth and infants born SGA, will be particularly important as we look to the future of

CHD outcomes. Additional studies focused on high-quality MFE data collection and large-scale studies exploring such factors on short- and long-term CHD outcomes are needed.

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Figures

Figure 1

National and State Deprivation Index Scores by Prematurity Status, Presence of Maternal Risk Factors, and SGA

shows box plots assessing national and state area deprivation index scores by prematurity status, presence of maternal risk factors (no= none identified, yes= at least 1 risk factor reported), and SGA (small for gestational age). Maternal risk factors include advanced maternal age (≥35 years old), smoking or illicit drug use, gestational or pregestational diabetes, gestational or pregestational hypertension, or obesity (body mass index ≥30kg/m^2). This figure shows consistently higher deprivation scores in the presence of prematurity, maternal risk factors, and SGA.