Human Milk and Direct Breastfeeding for Infants with Single Ventricle Congenital Heart Disease: An Analysis of Prevalence, Supportive and Limiting Factors, and Impact on Key Outcomes

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Dedication

This dissertation is dedicated to Inde Mark Elgersma (February 23, 2015–July 7, 2016), our beautiful child.

Abstract

Background

Infants with single ventricle congenital heart disease (SV CHD) undergo three staged palliative surgeries/interventions and are at risk for morbidity and mortality. Human milk (HM) and direct breastfeeding (BF) benefit other vulnerable neonates, but evidence about HM/BF for infants with SV CHD is limited. We aimed to:

(1) Determine HM/BF prevalence; determine whether BF at neonatal stage 1 palliation (S1P) discharge is associated with continued HM feeding at stage 2 palliation (S2P).

(2) Identify factors that support or limit HM and BF.

(3) Estimate the effect of HM and BF on key health outcomes.

Methods

We analyzed data from the National Pediatric Cardiology Quality Improvement Collaborative Registry (n=2491 infants; n=68 sites; 2016–2021). Analysis involved:

(1) Descriptive statistics for prevalence; adjusted logistic regression to examine associations between early BF/later HM.

(2) Machine learning to identify key HM/BF predictors.

(3) Poisson and logistic regression to compare outcomes between propensity-matched cohorts.

Results

(1) HM/BF prevalence was low and varied among sites. Infants BF at S1P discharge had 4.11 times greater odds of HM feeding at S2P.

(2) The strongest HM/BF predictor domain areas included preoperative feeding, demographics and social determinants of health, feeding route, clinical course, and site.

(3) Estimates for all outcomes were better in high HM/BF groups, including significantly lower odds of necrotizing enterocolitis, sepsis, and infection; shorter hospital length of stay; and lower

mortality.

Conclusions

Increasing the dose and duration of HM and BF has strong potential to substantially improve the health outcomes of these vulnerable infants.

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Chapter 1: Introduction

Congenital heart disease (CHD) is the most common congenital anomaly, affecting nearly 1 in 100 infants born in the United States (US).[1] Single ventricle (SV) physiology, in which a ventricle is underdeveloped or missing a valve, represents the most critical form CHD and incurs the highest hospital costs among birth defects.[1] These critically ill infants typically require three palliative childhood surgeries or catheter-based interventions including a high-risk neonatal stage 1 palliation (S1P) followed by stage 2 (S2P) at approximately 4–6 months of age. While CHD remains a leading cause of death for children in the US,[2] improved treatments have reduced mortality by up to 38%.[3] Most infants with SV CHD are now expected to survive past childhood, with consequent research and practice focus on optimizing development and improving quality of life for these infants and their families. Feeding is one primary developmental area of concern, as infants with SV CHD are at high risk for morbidity due to growth failure[4] and feeding-related complications such as necrotizing enterocolitis – a disease with 19–26% mortality in CHD.[5] Moreover, family caregivers experience enormous stress around feeding, often citing feeding as their number one concern.[6]

Human Milk and Direct Breastfeeding

Human milk (HM) feeding and direct breastfeeding (BF) are agreed upon as the normative, optimal nutrition for vulnerable infants by global[7] and national[8] health organizations, with exclusive HM considered a potentially "life-saving intervention"[9] for infants with CHD due to lowered risk for necrotizing enterocolitis.[10] Direct BF supports greater cardiorespiratory stability while feeding,[11] provides infant-specific immunological benefits,[12] and is preferred by most birthing persons.[13,14] However, little is known about HM and BF for infants with SV CHD. Previous studies have reported low prevalence of HM/BF in CHD populations[15–20] (eg, 21% exclusive HM feeding at initial hospital discharge[21] compared to US Healthy People goals of 42.4% exclusive HM feeding at 6 months of age[22]), but typically include heterogeneous CHD diagnoses and small samples from single centers. Given that infants with SV CHD

experience longer hospital stays and more complications than those with biventricular and non-critical CHD diagnoses,[23] it is important to determine whether the prevalence of HM and direct BF for infants with SV CHD differs from existing reports and to establish a baseline by which to measure future improvement in HM/BF feeding practices in this population.

Supportive and Limiting Factors

No previous studies have examined factors that support or limit HM feeding and direct BF for infants with any form of CHD. While factors associated with these feeding practices have been identified in other hospitalized neonatal populations (eg, infants born preterm),[24–26] infants with SV CHD may encounter unique challenges related to neonatal surgery, extensive time *nil per os* (ie, nothing by mouth), volume restriction due to parallel circulation, lengthy fortification, impaired mesenteric circulation, transition between neonatal and cardiac intensive care units, and historic provider discouragement of direct BF.[27–30] Based on a recent systematic review of risk factors for oral feeding problems in infants with critical CHD,[31] we hypothesized that factors related to diagnosis, site-specific practice, clinical course, and early (pre S1P) feeding practices are likely to be associated with establishment of HM feeding and/or direct BF for infants with SV CHD. Furthermore, demographic factors, social determinants of health, and disparities in healthcare access impact HM and BF prevalence in term and preterm infants,[24,25,32,33] but reporting of these factors has been neglected in studies on feeding for infants with CHD.[31] Research to identify factors that support or limit HM and BF in the SV CHD population is needed to highlight modifiable targets for improvement and to inform the development of culturally-responsive, family-centered interventions to improve the prevalence of HM and BF, with the potential to improve the health of these vulnerable infants.

Impact on Key Health Outcomes

Recent guidelines[7] have highlighted the importance of HM and direct BF in protecting the health and development of hospitalized infants. For preterm infants and those with surgical gastrointestinal

anomalies, HM/BF is associated with reduced incidence of necrotizing enterocolitis,[34–38] infection,[39] sepsis,[35,40–43] feeding-related complications,[40,42] and mortality,[44] along with shorter time to full feeds[40–42] and shorter hospital length of stay.[40,41,45] Little is known, however, about the impact of HM and BF on outcomes for infants with SV CHD. Two recent studies suggest that exclusive HM feeding before[10] and after[46] neonatal cardiac surgery may protect against necrotizing enterocolitis. However, only one of these studies[46] focused specifically on the SV CHD population, and the study's primary outcome was the impact of an HM-based fortifier on weight gain. A 2023 study[47] reported increased odds of postoperative infection associated with infant formula feeding, and described potential reductions in intensive care unit length of stay for infants fed HM following cardiac surgery for a variety of CHD diagnoses. This study was limited, however, by differences in age and surgical severity among feeding groups, and exhibited substantial bias in feeding group assignment based on maternal availability.

No additional previous research specifically examining the relationship between HM and health outcomes for infants with SV CHD has been identified. Furthermore, to our knowledge, there is no evidence about direct BF and outcomes for infants with CHD of any type. Thus, there is a critical gap in knowledge about HM/BF for infants with SV CHD. This gap in knowledge may contribute to the well-documented provider- and site-specific variation in feeding practice for infants with SV CHD,[48,49] which can lead to inconsistency in infant health outcomes[50] and can impede clear clinician-family communication.[6] For these vulnerable infants, who experience significant risk for hospital-associated disease and delay throughout the first year of life, an improved understanding of the potential benefits of HM feeding and direct BF is particularly urgent.

Summary

While HM and direct BF are broadly agreed upon as the normative, optimal nutrition for both healthy and sick infants, very little is known about HM and BF in the context of SV CHD. Foundational research is needed to describe the prevalence of HM and BF in this population, to identify factors that

support and limit HM and BF practices, and to determine potential causal relationships between these feeding practices and key health outcomes for infants with SV CHD.

Purpose

The primary purpose of this dissertation was to address the critical gap in knowledge about HM feeding and direct BF for infants with SV CHD. The dissertation manuscripts build evidence about HM and BF in this vulnerable population by establishing current HM and BF prevalence, identifying key factors that support and limit these feeding practices, and examining the impact of HM and direct BF on key outcomes that are crucial to the health and development of infants with SV CHD.

Dissertation Aims

Aim 1. To determine the prevalence of these practices at time points from birth through S2P surgery discharge and to test the hypothesis that direct BF at neonatal S1P discharge is associated with increased odds of HM feeding by any route at S2P. We hypothesized that the prevalence of HM feeding and direct BF would be below US and global recommendations, and that direct BF by S1P discharge would be associated with higher prevalence of HM feeding at S2P.

Aim 2. To identify factors that support or limit HM feeding and direct BF for infants with SV CHD at S1P discharge and at S2P. We hypothesized that variables related to diagnosis, surgical course, preoperative feeding practices, clinical site, demographics, social determinants of health, and disparities in healthcare access would be associated with HM/BF in the SV CHD population.

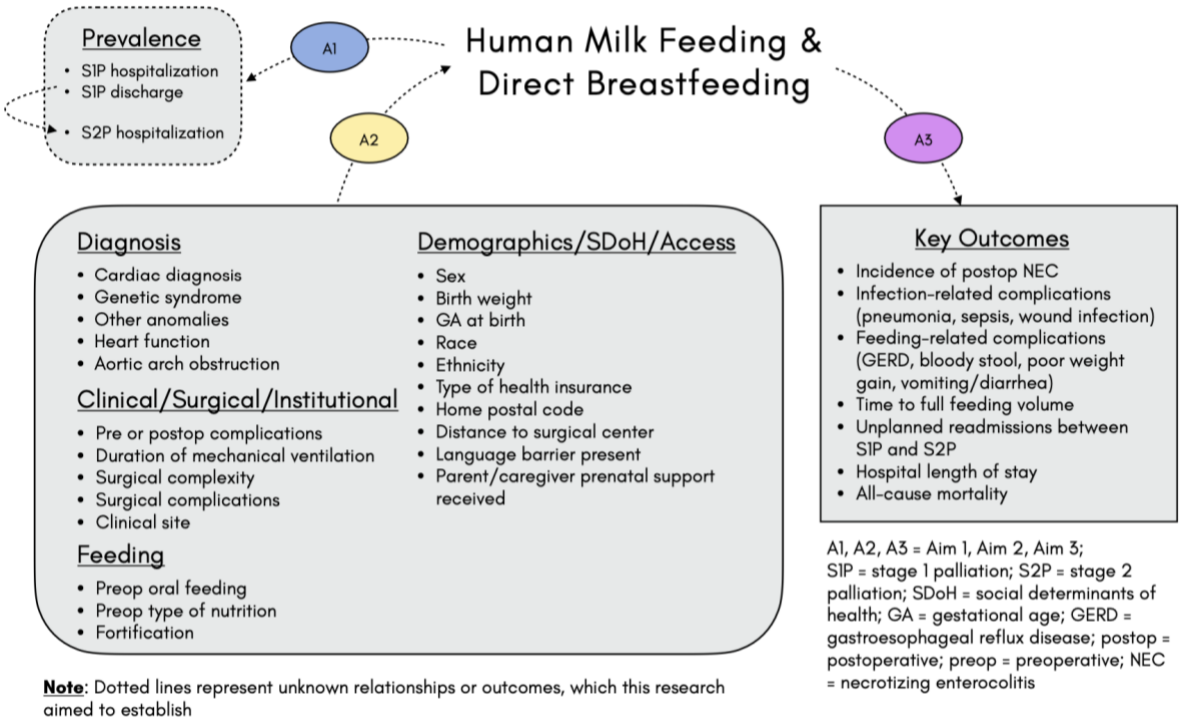
Aim 3. To estimate the effect of HM feeding and direct BF on key outcomes in a large, multisite, propensity score matched cohort of infants with SV CHD. We hypothesized that HM/BF would be associated with reduced prevalence of necrotizing enterocolitis and that we would identify additional benefits including reduced postoperative complications, time to full feeding volume, hospital length of stay, unplanned hospital readmission, and all-cause mortality.

Figure 1.1 provides a conceptual framework outlining the gaps in knowledge addressed by the dissertation aims.

Significance

This dissertation offers the first broadscale examination of HM feeding and direct BF for infants with SV CHD, and addresses common limitations of previous research by analyzing a multisite registry with the largest sample of this rare population to date. The research plan includes rigorous analytical methods including machine learning and propensity score matching to support causal inference which, to our knowledge, have not been used in feeding research for infants with CHD. Moreover, our examination of associations between HM/BF practices and demographics, social determinants of health, and disparities

Figure 1.1. Conceptual Framework for the Dissertation



in healthcare access includes important variables that have been strikingly neglected in previous CHD feeding research. The work presented in this dissertation substantially expands our previous knowledge

about HM feeding and direct BF for infants with SV CHD, supports the development of future family-centered interventions, and has the potential to improve the standard of care for these critically-ill children and their families.

Organization of Dissertation

The dissertation is organized into six chapters. Chapter 1 introduces the topic and outlines the purpose and aims of the dissertation. Chapter 2 is a systematic literature review evaluating current evidence regarding the impact of HM feeding on outcomes for infants with CHD. Chapter 3 reports the prevalence of HM feeding and direct BF for infants with SV CHD in the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) registry, and examines the association between early BF at S1P surgery discharge and later HM feeding by any route at S2P surgery. Chapter 4 describes a machine learning approach to identify predictors that support or limit HM feeding and direct BF for infants with SV CHD. Chapter 5 reports the results of a study examining the effect of HM feeding and direct BF on outcomes including necrotizing enterocolitis, sepsis, postoperative complications, length of stay, and mortality in propensity matched cohorts. Finally, Chapter 6 summarizes the dissertation findings, discusses the significance and novelty of the work, explores clinical implications of the findings, and offers recommendations for future research focus.

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Chapter 2: The Impact of Human Milk on Outcomes for Infants with Congenital Heart Disease: A Systematic Review

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Abstract

Background: Infants with congenital heart disease (CHD) are at risk for feeding-related morbidity and mortality, with growth failure and oral feeding problems associated with poor outcomes. The benefits of human milk (HM) for preterm infants have been well documented, but evidence on HM for infants with CHD has recently begun to emerge.

Objectives: Our primary aim was to examine the impact of HM feeding on outcomes for infants with CHD.

Methods: Following PRISMA guidelines, a search was conducted using MEDLINE, CINAHL, and Cochrane Database of Systematic Reviews. The quality of each study was assessed using the Joanna Briggs Critical Appraisal Tools. A total of 16 studies were included.

Results: There was evidence that an exclusive HM diet reduces the risk of necrotizing enterocolitis (NEC) for infants with CHD. Evidence with a higher risk for bias indicated that a well-managed HM diet may be associated with improved growth, shorter length of stay, and improved postoperative feeding and nutritional outcomes. Chylothorax outcomes were similar between modified HM and medium-chain triglyceride formula. The studies had significant limitations related to power, lack of control for covariates, and inconsistent delineation of feeding groups.

Conclusion: Based on the reduced risk for NEC and given the conclusive benefits in other vulnerable populations, we recommend that clinicians and institutions prioritize programs to support HM feeding for infants with CHD. Large, high-quality studies are needed to validate these results. Future work should clarify best practices in managing a HM diet to support optimal growth and development for these infants.

Introduction

Congenital heart disease (CHD) is the most common congenital anomaly, with nearly 1 in 100 infants affected.[1] Over the past 4 decades, surgical improvements have resulted in reductions in mortality of up to 38%.[2,3] Most children with CHD are now expected to survive to adulthood, and attention is turning to improvement of developmental outcomes, with feeding a major area of concern. Infants with CHD are at high risk for feeding-related morbidity and mortality, with growth failure and oral feeding problems associated with negative surgical and developmental outcomes.[4,5] Furthermore, family caregivers experience enormous stress around feeding, with feeding problems often cited as the number one concern – even above the cardiac condition.[6,7] Best practices for feeding infants with CHD are not well established, and there is documented variation in practice among providers and clinical sites.[8–10] This variation can lead to inconsistent and confusing communication about feeding practice between healthcare teams and family caregivers,[11,12] which may lead to decreased trust or confidence in the treatment team, compromised parental mental health, and negative consequences for infant outcomes.[11,13,14]

Human milk (HM) is considered the nutrition of choice by national and global health organizations.[15,16] For infants with CHD, multifactorial challenges related to clinical course, parent-infant separation, and lack of institutional support can lead to low rates of HM feeding and direct breastfeeding.[17–19] The benefits of HM for vulnerable infants in the neonatal intensive care unit (NICU) have been well documented,[20] but a body of evidence focused specifically on HM feeding for infants with CHD has only recently begun to emerge. A recently published Delphi study revealed general clinical consensus as to the importance of HM feeding in this population, but limited evidence to guide best practices, and highlighted the critical need for clinical guidelines on HM nutrition management for infants with CHD.[21] Currently, there is no systematic review examining associations between HM on outcomes for infants with CHD. A 2019 narrative review is informative,[22] but several relevant studies have been

published in the past 3 years and are not included in the 2019 review.

Therefore, the aim of this systematic review was to determine whether there are differences in outcomes for infants with CHD who receive HM feeding, as compared to other types of feeding. Secondary aims were to examine how HM feeding groups are defined in CHD infant feeding research, and to identify whether there are any harms associated with a HM diet in this population. By critiquing and synthesizing the available literature, this review provides evidence to inform clinical guidelines, and identifies gaps in the literature as foci for further study.

Methods

Operational definitions

For the purposes of this review, operational definitions are as follows: (1) "Infants" are children < 1 year of age; (2) "Congenital heart disease" is determined by confirmed clinical diagnosis; (3) "Human milk feeding" will be defined per study, and an examination of how this is defined is a secondary question of interest; (4) "Other types of feeding" will be defined per study and are may include formula feeding, bovine-based fortification, or nothing by mouth (*npo*); (5) "Outcomes" will not be defined *a priori*, but will be defined per study. Due to high variability in terminology, "human milk" will be used as an umbrella term to indicate mother's own milk (MOM) and/or donor HM, with the recognition that these two nutritional forms are not interchangeable.[23] An investigation of differences associated with route of nutrition (e.g., direct latch at the breast, bottle, nasogastric tube) is beyond the scope of this review.

Search strategy

Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[24] a literature search was conducted with the assistance of a university-based health sciences librarian, using MEDLINE (accessed via Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, 1946 to 2021), CINAHL, and Cochrane Database of Systematic Reviews. Key subject headings included "human milk," "breast feeding," "heart defects, congenital," "cardiac

surgical procedures," "infant," and "infant, newborn." Related keywords were added with truncation for maximum results. The search was limited to human subjects and English language results, and review articles were excluded. The full Ovid MEDLINE® search strategy can be seen in Table 2.1.

Table 2.1. Sample Search Strategy Using Ovid MEDLINE

Number	Query	Results
1	human milk.mp. or exp Milk, Human/	23641
2	breast feeding.mp. or exp Breast Feeding/	44114
3	(breast milk or breastmilk or breast fed or breastf*).mp.	46254
4	1 or 2 or 3	77313
5	exp Cardiac Surgical Procedures/ or exp Heart Defects, Congenital/	356045
6	(congenital heart or cardiac or cardi*).mp.	1556160
7	(hypoplastic or tetralogy or septal or transposition or coarc*).mp.	124650
8	single ventr*.mp.	4451
9	5 or 6 or 7 or 8	1754398
10	exp Infant/ or infant.mp. or exp Infant, Newborn/	1216883
11	(infant* or neonat* or baby or babies or newbor*).mp.	1528159
12	10 or 11	1528159
13	4 and 9 and 12	839
14	limit 13 to "review articles"	287
15	13 not 14	552
16	limit 15 to humans and English language	417

Notes: .mp = keyword search; exp " "/ = subject heading search; * = term truncation.

Study selection

Articles were imported into Rayyan QCRI[25] and duplicates were removed. An initial blinded screen by title and abstract was completed by two reviewers (KME and ACM). Studies that appeared to fit the inclusion criteria and those with abstracts without enough information to determine eligibility received a blinded full-text review by the same two reviewers. Reference lists of included studies were examined for additional eligible publications. Any disagreements were solved through consensus.

Articles were included in the review if (1) the study population was infants with clinically-diagnosed CHD; (2) the impact of HM on outcomes for infants with CHD was a primary or secondary focus; (3) the article reported findings from an original research study, including observational, quasi

experimental, or experimental designs. Conference abstracts were considered if there was enough information available to make a quality assessment. Articles were excluded if (1) the study population was focused on infants with a primary diagnosis other than CHD (e.g., a genetic syndrome); (2) the article was written in a language other than English; (3) the article was not original research (e.g., review, expert opinion); (4) the article reported findings from a case study or a quality improvement project. The search resulted in 483 records. After deduplication, title and abstract review, and full-text examination, 16 articles were included in the review. Figure 2.1 is a PRISMA flow diagram of the search process.

Data extraction and quality assessment

Data from included studies was extracted by one author (ACM) and validated by a second author (ALT or KMS). Information collected included citation, study methods, sample characteristics, results, limitations, and funding sources. First authors were contacted for missing data.

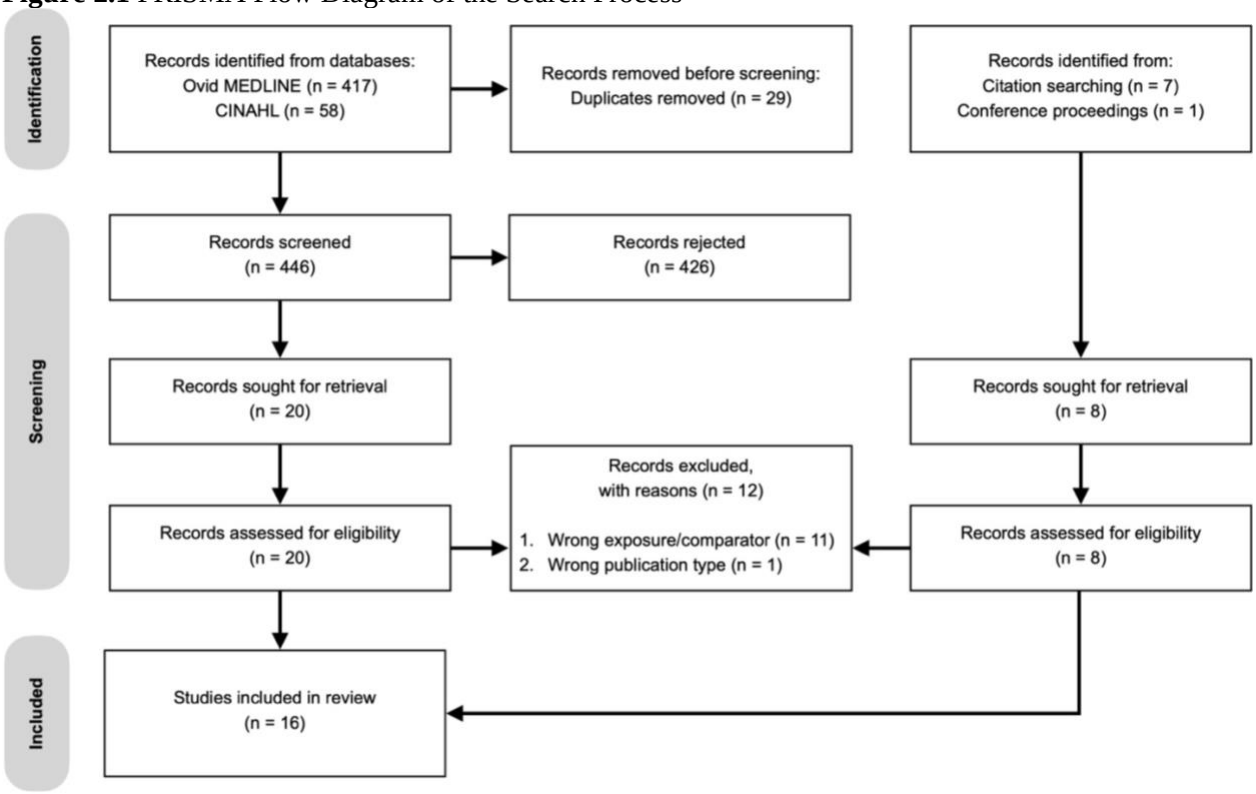
The methodological quality of each study was assessed using Critical Appraisal Tools from the Joanna Briggs Institute.[26] These are a collection of reliable, validated, design-specific tools that can be used to evaluate the quality of observational, quasi experimental, and experimental studies. An initial quality assessment was conducted by the first author (KME), with a second, blinded assessment by an additional author (ACM, ENS, NMS, or KMS). Any disagreements were solved through consensus.

Results

Study characteristics

A total of 16 articles met the final inclusion criteria. Nine were cohort studies (7 retrospective[27–33] and 2 prospective[34,35]), 4 featured a quasi-experimental design,[36–39] 2 were randomized controlled trials (RCTs),[40,41] and 1 was a retrospective case-control design.[19] One RCT included multiple sites,[40] and 2 studies were secondary analyses of multisite data sets.[19,32] The studies took place most often in the United States (n = 10), with Canada (n = 3), China (n = 1), Germany (n = 1), and Italy (n = 1) also represented. A summary of characteristics of the included studies can be found in Table 2.2.

Figure 2.1 PRISMA Flow Diagram of the Search Process



Abbreviation: CINAHL = Cumulative Index to Nursing and Allied Health Literature.

Sample

There were a total of 8176 participants in the 16 included studies. These participants were newborns diagnosed with complex CHD,[27,29,32] medically stable newborns with CHD,[34] infants undergoing cardiac surgery for CHD,[19,30,31,33,35,38,40,41] or infants with CHD diagnosed with chylothorax after surgery.[28,36,37,39] Participants were 60.3% male and 39.7% female (female sex was often presumed, as only 6 studies reported female numbers). Only 7 studies reported details of race and ethnicity.[19,27–29,32,33,35] Of 7659 infants, 56.5% identified as white, 26.5% Hispanic, 11.7% Black, 0.3% Asian, and 5.0% other. Social determinants of health were reported in 3 studies, with Kocel et al.[36] and Siemienski[35] detailing parental level of education, and McCrary et al.[33] reporting the percentage of patients receiving Medicaid.

Table 2.2. Summary Description of Included Studies

First author (Year) / Country	Sample size / Study design	Population / Timing	Outcomes of interest	Results summary	Human milk definition[a] / Feeding groups	Major limitations
Becker (2015) / United States	6710 / Retrospective cohort	Infants with CHD treated with PGE / Birth–NICU discharge	• NEC	∅	BM: Exposure to MOM or DHM on day of interest / BM fed; formula fed	Very low numbers with NEC; majority of feeding data for infants with NEC missing; only looked at feeding on day of diagnosis
Boctor (1999) / Canada	24 / Retrospective cohort	Full term infants < 1 year undergoing cardiac surgery / Postoperative non-ICU stay	• Daily weight change • Median weight change • Weight-for-length	Exclusively breastfed infants may have lower weight change; significance unclear	"Breastfed" not defined; 6/10 infants in breastfed group supplemented with formula by bottle / Breastfed; formula fed; formula + solid food	Small n; no description of analysis; no baseline demographics or measurements; straight weight gain/loss is not meaningful without adjustment for confounders
Blanco (2021) / United States	84 / RCT	Term infants undergoing neonatal cardiac surgery / Birth–follow up ongoing	• Weight, length, and HC velocity • NEC • LOS • Sepsis • Calorie concentration tolerated	HM fortified with HM-based fortifier had improved short-term growth, increased caloric intake, decreased risk of NEC	HM: MOM or DHM / HM fortified with Prolacta human milk fortifier; HM and/or formula, fortified with bovine fortifier	Only conference presentation available; limited information about power and exclusion criteria
Combs (1993) / United States	50 / Prospective cohort	Stable newborns with CHD / 5 months post discharge	• Weight gain	Bottle fed infants (100% formula) fell further off their growth curves	"Breastfed" is any amount of MOM / Breastfed vs. bottle fed	No power; statistics not described; feeding groups are not clearly delineated; no diagnosis information
Cognata (2019) / United States	546 / Retrospective cohort	Newborns with DD BiV, SV, or other complex CHD / Preoperative stay	• NEC	An exclusive unfortified HM diet lowered the risk for NEC	HM: MOM or DHM / Exclusive unfortified HM diet; any formula; received fortification	Not powered to fully evaluate risk for all stages of NEC

First author (Year) / Country	Sample size / Study design	Population / Timing	Outcomes of interest	Results summary	Human milk definition[a] / Feeding groups	Major limitations
DiLauro (2020) / Canada	24 / Quasi experimental[b]	Infants <12 months with chylothorax after cardiac surgery / Until treatment concluded	• Duration of feeding intervention • Feeding intolerance • Volume; duration CT drainage • Weight gain • Change in WAZ; LAZ; HAZ	∅	Modified BM: Defatted BM (MOM or DHM); had ≥ 50% of feeds as HM before study / Modified BM: target fortification; Modified BM: higher initial concentration; MCT formula	Small n, not fully powered. Some unstable patients (greatest risk for growth failure) not included; modified BM group varied in BM dose
Fogg (2016) / United States	35 / Retrospective cohort	Infants < 90 days of with chylothorax after cardiac surgery / Until treatment concluded	• Duration of CT • Duration of ventilation • Re-accumulation of chylothorax • Hospital and ICU readmissions • LOS • Hospital deaths • Growth velocity	∅ Trend toward higher discharge WAZ in defatted HM group	Defatted HM: MOM; must have had ≥ 75 % of feeds as HM before study initiation; Unclear if any were supplemented by formula / Defatted HM; MCT formula	Small n, limited power; caloric density of feedings frequently adjusted, but not controlled in analysis
Kataria-Hale (2021) / United States	399 / Retrospective cohort	Newborns with DD BiV, SV, or other complex CHD / Until discharge	• Postoperative NEC • Hospital LOS • Days to full feeding	Preoperative nutrition type does not impact incidence of postoperative NEC	HM: MOM and/or DHM / Preoperative HM; preoperative unfortified formula	Small number of NEC cases; differences between groups not described; dose of HM not recorded, may have varied
Kocel (2016) / Canada	16 / Quasi experimental	Infants <12 months with chylothorax after cardiac surgery / Until treatment concluded	• Volume; duration CT drainage • Weight gain • Change in WAZ; LAZ; HAZ • Feeding intolerance	The modified BM group experienced declines in WAZ and LAZ; MCT group had an increase in HAZ	Modified BM: MOM; had ≥ 80% of feeds as HM before surgery; fortified with either HM fortifier and MCT oil or MCT formula, + soybean oil / Modified BM; MCT formula	Small n, not fully powered for all outcomes. BM dose varied (range, 45%–100%)
Lopez (2018) / United States	228 / Retrospective case-control	Infants with HLHS / To stage 2 palliation	• NEC	Infants who developed NEC had higher rates of formula only feeding at discharge	BM: Not defined / BM; formula; combination	HM outcomes not primary focus; feeding group not reported preop; large registry, can't be sure of reliable data

First author (Year) / Country	Sample size / Study design	Population / Timing	Outcomes of interest	Results summary	Human milk definition[a] / Feeding groups	Major limitations
McCrary (2013) / United States	133 / Retrospective cohort	Neonates with modified systemic-to-pulmonary artery shunts / To shunt takedown	• WAZ at surgery, first clinic visit, and shunt takedown	∅ Trend toward lower WAZ in group with no BM	BM: Not defined / Any BM; none	No clear delineation between feeding groups; feeding data not reliably recorded; no power analysis
Neumann (2020) / Germany	23 / Quasi experimental	Infants with chylothorax after cardiac surgery / 3 months after diagnosis	• Volume; duration CT drainage • Duration of postoperative CT; low-fat diet; tube feeding • Hospital & ICU LOS • Change in WAZ; LAZ; HAZ	Duration of low-fat diet days lower in the low-fat BM group	Low-fat BM (MOM) + MCT oil / Low-fat BM + MCT oil; MCT formula	Small n, no power analysis, no control of confounders.
Rosti (2011) / Italy	122 / Retrospective cohort	Neonates <30 days undergoing cardiac surgery; complicated clinical course excluded / Postoperative hospital stay	• Hospital & ICU LOS • Weight gain	∅	MOM / MOM; starting formula (67 kcal/100mL); high-calorie preterm formula (80 kcal/100mL)	No power analysis; no control of confounders; short follow-up time (mean < 1 week); nutrition choices unclear; not generalizable to complex cases
Siemienski (2019) / United States	75 / Prospective cohort	Neonates undergoing cardiac surgery; mother planning to breastfeed / 12 months old	• WAZ; WLZ; LAZ; HAZ change over time	∅	BM predominant = BM (MOM or DHM) as predominant source of nutrition throughout the first year of life / BM predominant; mix of BM and formula; BM moving to mostly formula	Small n in each group; no power analysis; missing data
Yu (2020)	56 /	Infants undergoing cardiac surgery;	• Prealbumin & albumin levels	BM group significantly better in all outcomes	BM: MOM /	No control of confounders; categorical analysis likely

First author (Year) / Country	Sample size / Study design	Population / Timing	Outcomes of interest	Results summary	Human milk definition[a] / Feeding groups	Major limitations
/ China	Quasi experimental[c]	staged surgery excluded / Post-operative hospital stay	• Hypoglycemia & hypocalcemia • Anemia • Time to start feeding; total EN • Average daily weight gain • Duration of ventilation • Hospital & ICU LOS • Feeding intolerance • Dyspeptic diarrhea • Nosocomial infection	except hypoglycemia, hypocalcemia, and duration of mechanical ventilation, which were non-significant	BM fed; formula fed	inappropriate; complex CHD excluded; possible unexplored group differences (e.g., formula fed infants were from rural areas; parents couldn't travel to provide HM)
Zyblewski (2015) / United States	27 / RCT (pilot)	Neonates undergoing cardiac surgery / To discharge	• L/M ratio	∅	Not defined / Trophic BM feeds; NPO	Small n; not powered for significance (pilot); sickest patients excluded

Abbreviations: BiV = biventricular physiology; BM = breast milk; CHD = congenital heart disease; CT = chest tube; DD = ductal dependent; DHM = donor human milk; HAZ = head circumference-for-age z-score; HC = head circumference; HLHS = hypoplastic left heart syndrome; HM = human milk; ICU = intensive care unit; L/M = lactulose/mannitol; LAZ = length-for-age z-score; LOS = length of stay; MCT = medium chain triglyceride; MOM = mother's own milk; NEC = necrotizing enterocolitis; NICU = neonatal intensive care unit; NPO = nothing by mouth; PGE = prostaglandin E1; RCT = randomized controlled trial; SV = single ventricle physiology; WAZ = weight-for-age z-score; WLZ = weight-for-length z-score.
∅ = no significant differences.
[a]Due to variability in terminology, we have opted to use human milk as a general term representing mother's own milk (MOM) and/or donor human milk (DHM). The specific terminology used by each study is reported in this column, with a description as provided by the authors. Whenever possible, we have indicated when the study differentiates between MOM and DHM.
[b]Study was an open-label clinical trial; participants receiving ≥50% of feeds as HM were randomized to one of two modified HM groups; others assigned to the MCT formula group.
[c]The authors categorize this as a retrospective study; however, participants were prospectively enrolled and assigned to a modified HM group or a formula feeding group.

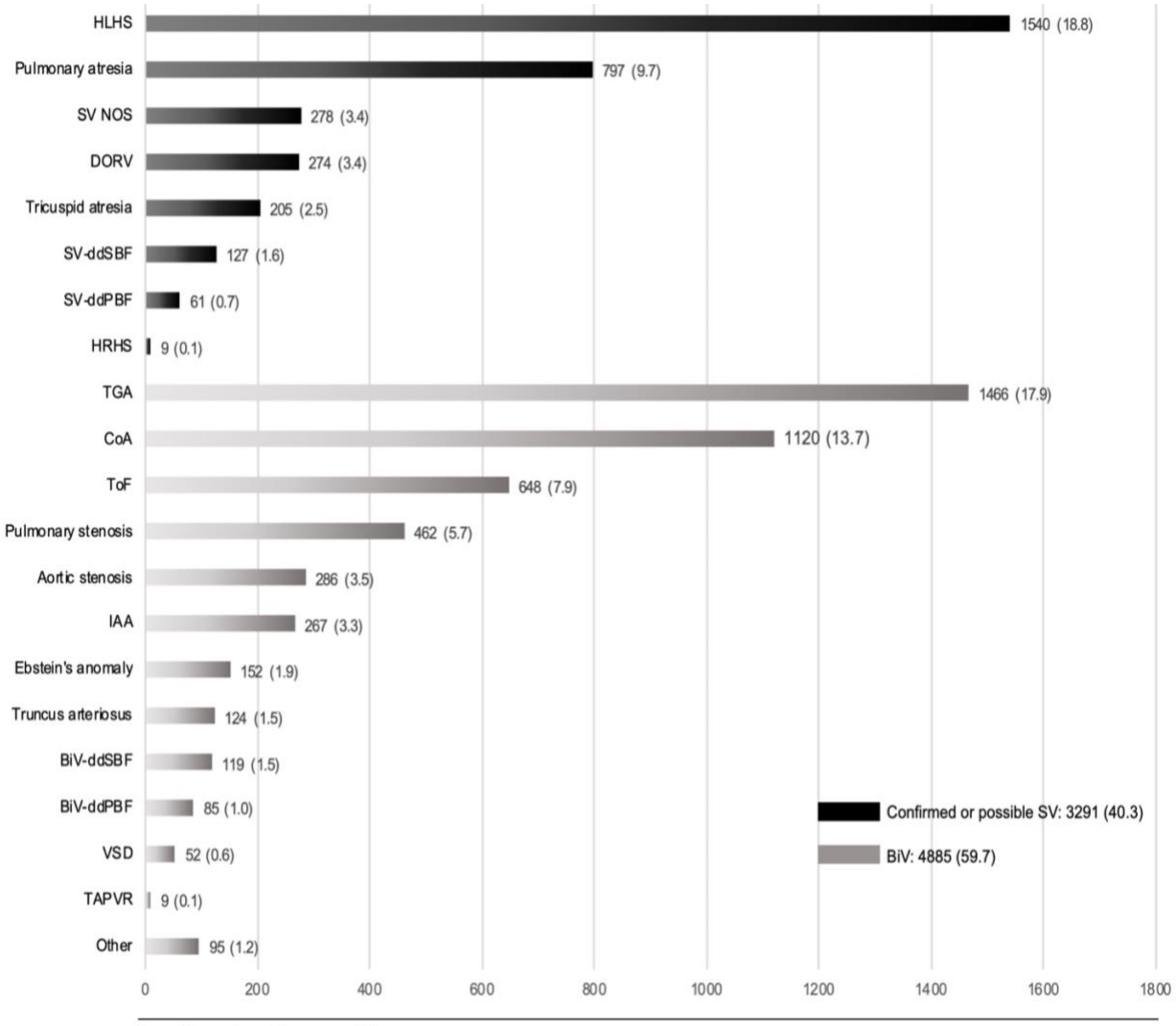
The age of the participants was most often reported at 3 timepoints, depending on the study aim: Gestational age, age at surgery, and/or age at chylothorax diagnosis. The mean or median gestational age was > 37 weeks in 11 studies,[19,27–30,33,36,37,39–41] > 36 weeks in another,[32] and unreported in 4 studies.[31,34,35,38] Age at surgery was mean or median < 3 months for all 5 studies reporting this metric.[28,31,33,38,41] Age at chylothorax diagnosis varied, with 4 studies reporting a median range of 0.6 months–5.3 months.[28,31,36,37]

Weight was also reported at the same 3 timepoints. The mean or median birth weight was > 3.0 kg in 7 studies,[19,28–30,36,39,41] while Rosti et al. reported a birth weight range of 2.1 kg–4.1 kg.[30] Two other studies reported birth weights as percentages, with 77.4% > 2.5 kg in Becker et al.,[32] and 93.4% > 2.0 kg in Cognata et al.[27] Blanco et al. reported that 86.9% of infants were average or large for gestational age,[40] and the remaining 5 studies did not report birth weight.[31,33–35,38] Mean weight at surgery ranged from 2.6 kg–4.0 kg in the 3 studies that provided these data,[28,30,38] while McCrary et al. reported a mean weight-for-age z-score (WAZ) at initial shunt placement of -0.61.[33] Mean weight at chylothorax diagnosis varied, from 3.2 kg–5.9 kg.[36,37,39]

Three studies provide information about length and head circumference at birth and/or chylothorax diagnosis.[36,37,39] The median length at birth ranged from 47.5 cm –51.0 cm,[37,39] while median length at diagnosis was between 51.0 cm–61.1 cm.[36,37,39] The mean or median head circumference at diagnosis ranged from 34 cm–39.3 cm.[36,37,39]

CHD diagnoses included both single ventricle (SV; *n*, % 3291, 40.3) and biventricular (BiV; 4885, 59.7) defects. Transposition of the great arteries was the most common BiV diagnosis, and hypoplastic left heart syndrome the most common SV physiology. Information about the diagnoses of the sample can be found in Figure 2.2.

Figure 2.2. Primary Cardiac Diagnoses of Participants in the Included Studies



Abbreviations: CoA = coarctation of the aorta; ddSBF = ductal-dependent systemic blood flow; ddPBF = ductal-dependent pulmonary blood flow; DORV = double outlet right ventricle; HLHS = hypoplastic left heart syndrome; HRHS = hypoplastic right heart syndrome; IAA = interrupted aortic arch; NOS = not otherwise specified; SV = single ventricle; TAPVR = total anomalous pulmonary venous return; TGA = transposition of the great arteries; ToF = tetralogy of Fallot; VSD = ventricular septal defect.
Note: All numbers given are n (%).

Exclusion criteria varied among studies. Eight studies excluded infants with non-cardiac congenital anomalies or genetic syndromes,[27,29,30,35,38–41] and 2 studies excluded premature infants born < 32 weeks.[33,37] Three studies excluded infants with non-complex CHD (e.g., not requiring intervention or prostaglandin E1 infusion),[27,29,32] while Yu et al. excluded infants with complex CHD requiring staged

surgery.[38] Six studies excluded infants who experienced a complicated clinical course or death (e.g., preoperative necrotizing enterocolitis [NEC], chylothorax, extracorporeal membrane oxygenation, hemodynamic instability, or no enteral feeding).[29,30,36,38,40,41]

Human milk feeding definitions

In 6 studies, infants in HM feeding groups received 100% MOM or donor HM.[27,29,30,32,38,40] In one of these, infants in the HM feeding group received HM-based fortifier (Prolacta), while the comparison group received bovine-based fortifier.[40] Two additional studies implied that HM feeding groups received 100% HM, but were unclear regarding MOM, donor HM, and/or fortification.[19,41] Four studies on treatment of chylothorax defined HM feeding groups as receiving low-fat MOM or donor HM with some type of fortification, such as MCT oil, MCT formula, soybean oil, or bovine-based HM fortifier.[28,36,37,39] Three of these studies considered varying amounts of formula supplementation acceptable in a HM diet, with ≥50%,[39] ≥ 75%,[28] or ≥ 80%[36] required for HM feeding group eligibility. Siemienski defined a "breast milk predominant" group as receiving primarily HM (defined as MOM or donor HM) throughout the first year of life.[35] In the final 3 studies, HM feeding was not clearly defined and allowed for any amount of HM, which led to a lack of differentiation between groups.[31,33,34] For example, in Boctor et al., 6 out of 10 infants in a "breastfed" group were fed MOM supplemented with formula, with no information available about HM dose.[31] Combs and Marino defined "breastfed" as any amount of MOM,[34] while McCrary et al. compared infants with any "breast milk use" (with MOM or donor HM unspecified) to those with none.[33]

Findings

Outcomes examined in the studies can be grouped into four main categories: (1) incidence of NEC, (2) outcomes related to treatment of chylothorax, (3) weight gain, and (4) other postoperative outcomes. All significant results with point estimates can be found in Table 2.3.

Necrotizing enterocolitis. Six studies examined associations between a HM diet and NEC.[19,27,29,32,40,41] A HM diet was associated with a lower incidence in NEC in 5 studies, with 3 results

Table 2.3. All Significant Outcomes Found in Included Studies, With Effect Size

First author (Year)	Outcome	Analysis	Exposure/intervention vs. comparator[a]	Effect size	p value
Necrotizing enterocolitis					
Blanco (2021)	NEC (Bell stages I, II)	Bivariate (not specified)	HM (MOM or DHM) with HM-based fortifier (Prolacta) vs. HM (MOM, DHM) or formula with bovine fortifier	2 (3.6) vs. 8 (15.4)[f]	p = 0.04
Cognata (2019)	NEC (Bell stages I-III)	Multivariable linear regression	Exclusive unfortified HM diet (MOM or DHM) vs. formula feeding or fortification	0.17 (0.04–0.84)[g]	p = 0.03
Lopez (2018)	NEC (staging not specified)[b]	Chi-square test	NEC: BM; formula; mix vs. No NEC: BM; formula, mix	10 (18); 35 (61); 12 (21) vs. 24 (14); 39 (29); 98 (57)[f]	p < 0.01
Chylothorax					
Neumann (2020)	Duration of treatment	t-test	Low-fat BM (MOM) vs. MCT formula	41 (5) vs. 67 (58)[h]	p = 0.036
Kocel (2016)	Change in WAZ (from baseline)	t-test	Modified BM (MOM) vs. MCT formula	-0.76 (1.25) vs. -0.08 (0.85)[h]	p = 0.04 vs. p = ns
Kocel (2016)	Change in LAZ (from baseline)	t-test	Modified BM (MOM) vs. MCT formula	-0.44 (1.09) vs. 0.02 (0.76)[h]	p = 0.01 vs. p = ns
Kocel (2016)	Change in HAZ (from baseline)	t-test	Modified BM (MOM) vs. MCT formula	-0.17 (1.02) vs. 0.59 (0.59)[h]	p = ns vs. p = 0.03
Weight gain					
Blanco (2021)	Weight velocity, birth to end of study (g/kg/day)	Wilcoxon rank-sum test	HM (MOM or DHM) with HM-based fortifier (Prolacta) vs. HM (MOM, DHM) or formula with bovine fortifier	3.62 (1.88, 5.33) vs. 2.79 (0.54, 4.16)[i]	p = 0.04
Boctor (1999)	Weight change at discharge (g/day)	Not specified	Exclusively BF vs. BF + bottle vs. bottle	-49 (-80, -23) vs. 5 (-83, 43) vs. 20 (-100, 73)[j]	p = 0.04
Combs (1993)	Weight loss >20% birth to 5 months	Chi-square test	BF (MOM) vs. bottle	6 (46) vs. 15 (83)[f]	p = 0.04
Yu (2020)	Average daily postop weight gain (g/kg/day)	t-test	BMF (MOM) vs. formula	19.0 (3.4) vs. 14.4 (2.3)[h]	p = 0.041
Postoperative outcomes: Length of stay					
Yu (2020)	Length of ICU stay (days)	t-test	BMF (MOM) vs. formula	6.0 (2.2) vs. 8.1 (2.9)[h]	p = 0.045
Yu (2020)	Length of hospital stay (days)	t-test	BMF (MOM) vs. formula	13.9 (4.2) vs. 17.8 (5.6)[h]	p = 0.037

Postoperative outcomes: Nutrition and feeding outcomes					
Yu (2020)	Prealbumin (mg/L)[c]	t-test	BMF (MOM) vs. formula	147.3 (15.2) vs. 121.5 (18.3)[h]	p = 0.029
Yu (2020)	Albumin (g/L)[c]	t-test	BMF (MOM) vs. formula	46.4 (4.2) vs. 40.5 (5.1)[h]	p = 0.034
Yu (2020)	Anemia	Chi-square test	BMF (MOM) vs. formula	1 (4) vs. 6 (21)[f]	p = 0.043
Yu (2020)	Start of feeding time (hours)	t-test	BMF (MOM) vs. formula	27.8 (7.4) vs. 50.4 (13.7)[h]	p = 0.022
Yu (2020)	Achieved total enteral nutrition (days)	t-test	BMF (MOM) vs. formula	3.0 (1.2) vs. 5.2 (2.1)[h]	p = 0.038
Postoperative outcomes: Complications					
Yu (2020)	Feeding intolerance[d]	Chi-square test	BMF (MOM) vs. formula	1 (4) vs. 7 (25)[f]	p = 0.022
Yu (2020)	Dyspeptic diarrhea[e]	Chi-square test	BMF (MOM) vs. formula	0 (0) vs. 4 (14)[f]	p = 0.038
Yu (2020)	Nosocomial infection	Chi-square test	BMF (MOM) vs. formula	1 (4) vs. 6 (21)[f]	p = 0.043

Abbreviations: NEC = Necrotizing enterocolitis; WAZ = weight-for-age z-score; LAZ = length-for-age z-score; HAZ = head circumference- for-age z-score; ICU = intensive care unit; HM = human milk; MOM = mother's own milk; DHM = donor human milk; BM = breast milk; MCT = medium-chain triglyceride; BF = breastfed; BMF = breast milk fed.

[a]The terminology used for feeding types is per the authors of each individual paper. Specification regarding mother's own milk and/or donor human milk is provided in parentheses, whenever possible. If the authors were unclear as to the source of the human milk, the original terminology is provided. Additional details about study definitions of human milk feeding groups are available in Table 2.2.

[b]At stage 1 palliation surgery discharge.

[c]No difference at baseline.

[d]Feeding intolerance is defined as: The infants had symptoms, such as gastric retention and vomiting, and gastric retention was more than 50% of the previous total feeding amount. Physical examination revealed increased bowel sounds and abnormal abdominal tenderness.

[e]Dyspeptic diarrhea is defined as: Defecation multiple times a day, mostly in the morning or after feeding, and mushy and watery stool, with a pungent odor.

[f]n (%).

[g]OR (95% CI).

[h]Mean (SD).

[i]Median (IQR).

[j]Median (range).

reaching significance.[19,27,40] Cognata et al. found that an exclusive unfortified HM diet resulted in 83% lower odds of preoperative NEC, after controlling for cardiac lesion, race, feeding volume, small for gestational age birth weight, inotrope use, and prematurity.[27] Blanco et al. reported a reduced incidence of NEC and suspected NEC in infants receiving HM plus HM-based fortifier, as compared to HM or formula plus bovine fortifier (3.6% vs. 15.4% incidence),[40] while Lopez et al. found that infants with HLHS who developed NEC during the initial hospitalization were more likely to be receiving an exclusive formula diet at hospital discharge (n = 35, 61%) than those without NEC (n = 39, 29%).[19] The

only study that reported a higher incidence of NEC in a HM feeding group had only 3 infants who developed the disease (2 in a trophic HM group, 1 *nil per os*).[41] In Cognata et al.[27] and Kataria-Hale et al.[29] a diagnosis of NEC was determined by Bell's modified criteria and reviewed by 2 neonatologists and a radiologist to determine staging. Blanco et al.[40] and Zyblewski et al.[41] reported the modified Bell stage of the NEC cases examined, but did not provide details about who determined the diagnosis.[40,41] Lopez et al.[19] and Becker et al.[32] completed secondary analyses of large national registries and were not able to verify a uniform grading system for diagnosing NEC.

Chylothorax. Four studies focused on outcomes related to treatment of chylothorax with modified HM, as compared to medium chain triglyceride (MCT) formula.[28,36,37,39] Two studies examining duration of treatment found that infants receiving modified HM experienced shorter treatment,[37,39] with the result in Neumann et al. reaching significance (41 days vs. 67 days).[37] Two studies investigating number of chest tube drainage days reported conflicting results, but neither was significant.[28,36] Similarly, 3 studies recorded volume of chest tube drainage with inconclusive results.[36,37,39] Hospital length of stay (LOS) was examined in 2 studies, with infants in the modified HM group experiencing a shorter LOS in both; however, differences were not significant.[28,37]

Changes in anthropomorphic measurements from chylothorax diagnosis to treatment end were examined in 4 studies, with mixed results.[28,36,37,39] Kocel et al. found significant decreases in WAZ (-0.76) and length-for-age z-score (LAZ; -0.44) in the modified HM group, but not in the MCT group.[36] Similarly, the head circumference-for-age z-score (HAZ) increased in the MCT group (0.59), but not in the modified HM group.[26] In contrast, Fogg et al. reported a trend toward higher absolute growth velocity from baseline to discharge in the modified HM group,[28] while DiLauro et al. and Neumann et al. found no differences in any anthropomorphic measurements between feeding groups.[37,39] Taken as a whole, most results related to physical growth during treatment for chylothorax were inconclusive.

Weight gain. Seven studies described weight-related outcomes,[30,31,33–35,38,40] with findings in 4

studies reaching significance.[31,34,38,40] Of these, 3 demonstrated improved outcomes for infants in HM feeding groups.[34,38,40] Yu et al. reported improved average daily weight gain for postoperative infants receiving a HM diet (19.0 vs. 14.4 g/kg/day),[38] while Combs & Marino found that, by 5 months after discharge, more infants who were bottle fed experienced >20% negative change in weight percentile (83% vs. 46%).[34] Blanco et al. reported that, from birth to the end of the study period, infants fed HM-based fortifier experienced a higher median weight velocity than those fed with bovine fortifier (3.62 vs. 2.79 g/kg/day).[40] In contrast, Boctor et al. found significant differences in median weight change at discharge between infants who were exclusively directly breastfed (-49 g/day), fed a combination of HM and formula (5 g/day), or 100% formula fed (20 g/day).[31] The results in McCrary et al. did not reach significance, but trended toward a higher WAZ for palliated infants in the HM feeding group at the first clinic visit after discharge (-1.5 vs. -1.78, $p = 0.12$), and at shunt takedown (-1.21 vs. -1.60, $p = 0.058$).[33] The remaining 2 studies found no difference between feeding groups.[30,35]

Other postoperative outcomes. HM feeding was associated with a shorter postoperative LOS in 5 of the 6 studies examining this outcome.[28–30,37,38,40] Only the results in Yu et al. reached statistical significance, with shorter hospital (13.9 vs. 17.8 days) and intensive care unit (ICU, 6.0 vs. 8.1 days) LOS for the HM feeding group.[38] Yu et al. also found that infants fed with HM were started on enteral feeds earlier (27.8 vs. 50.4 hours), and achieved full feeds in 3.0 vs. 5.2 days.[38] Infants in this study also experienced improved outcomes in several markers of nutritional status (prealbumin, albumin, anemia) and incidence of complications (feeding intolerance, dyspeptic diarrhea, nosocomial infection).[38] Additional information about these outcomes can be found in Table 2.3.

Quality of evidence

The quality of evidence of each of the included articles was appraised using the Joanna Briggs Critical Appraisal Tools,[26] with results presented in Table 2.4. It should be noted that the quality assessment was focused solely on the strength of evidence as related to HM feeding and outcomes for

Table 2.4. Quality Assessment Using the Johanna Briggs Institute Critical Appraisal Tools[a]

	Becker, 2015	Boctor, 1999	Cognata, 2019	Combs, 1993	Fogg, 2016	Kataria-Hale, 2021	McCrary, 2013	Rosti, 2011	Siemienski, 2019
Cohort studies									
Groups similar?	?	?	?	?	X	?	?	✓	?
Exposures measured similarly?	?	?	✓	✓	✓	?	?	?	✓
Exposures measured reliably?	X	X	?	X	?	?	X	?	X
Confounding factors identified?	X	X	✓	X	✓	✓	X	X	X
Strategies for confounding factors?	X	X	✓	X	✓	✓	X	X	X
Groups free of the outcome at the start?	?	?	✓	?	✓	✓	?	?	✓
Outcomes measured reliably?[b]	?	?	✓	X	?	✓	?	?	?
Follow up time sufficient?	✓	?	✓	✓	✓	✓	✓	✓	✓
Follow up complete?				X					X
Strategies for incomplete follow up?				X					X
Appropriate statistical analysis?	?	?	✓	?	?	✓	?	?	?

	Lopez, 2018
Case-control studies	
Groups comparable?	✓
Cases and controls matched?	✓
Same criteria used to identify cases and controls?	✓
Exposures measured reliably?	?
Exposures measured similarly?	?
Confounding factors identified?	X
Strategies for confounding factors?	X
Outcomes measured reliably?	?
Exposure period long enough?	✓
Appropriate statistical analysis?	✓

	DiLauro, 2020	Kocel, 2016	Neumann, 2020	Yu, 2020		Blanco, 2021	Zyblewski, 2015	
Quasi-experimental studies					**Experimental studies**			**Notes**
Clear cause and effect?	✓	✓	✓	✓	True randomization?	✓	✓	[a]*https://jbi.global/critical-appraisal-tools.*
Groups similar?	✓	✓	✓	✓	Allocation concealed?	?	?	[b]Reasons for an "unclear" or "no" rating as to the reliability of outcome measurements in all study designs were generally related to diagnosis criteria for NEC or means of weight/anthropomorphic measures. Regarding NEC diagnosis, Becker et al. and Lopez et al. did not use a standardized grading system (e.g., modified Bell staging). Regarding weight or anthropomorphic measurements: Blanco et al., Boctor et al., Fogg et al., McCrary et al., Neumann et al., Rosti et al., Siemienski et al., and Yu et al. either rely on retrospective chart data, which is subject to inconsistency, or do not describe a standardized process of measurement. The study from Combs & Marino included weights from maternal self-report, with no standardization of measurement.
Groups received similar care, except for exposure/intervention?	?	?	✓	✓	Groups similar?	✓	✓	
Control group?	✓	✓	✓	✓	Participants blinded?	✓	X	
Multiple outcome measures pre and post?	✓	✓	✓	X	Those delivering treatment blinded?	X	X	
Follow up complete and/or analyzed?	X	✓	✓	✓	Outcomes assessors blinded?	?	X	
Outcomes measured similarly between groups?	✓	✓	?	?	Groups received similar care, except for exposure/intervention?	✓	✓	
Outcomes measured reliably?	✓	✓	?	?	Follow up complete or analyzed?	X	?	
Appropriate statistical analysis?	✓	?	?	X	Analyzed by intention to treat?	✓	✓	
					Outcomes measured similarly between groups?	✓	✓	
					Outcomes measured reliably?	?	✓	
					Appropriate statistical analysis?	?	?	✓ = yes, X = no, ? = unclear.
					Trial design appropriate and deviations accounted for?	✓	✓	

infants with CHD, which was not a primary focus of all studies. The assessment does not necessarily reflect the strength of studies in regard to other outcomes.

As a group, the HM findings from the 16 studies exhibited methodological issues which call into question the validity of the results. Only 4 studies described clear, reliable outcomes measures (e.g., diagnosis of NEC, methods to track weight or other anthropomorphic measurements, etc.).[27,29,36,39] Seven of the 9 cohort studies were retrospective chart reviews,[27–33] with inherent bias in data collection due to potential differences in accuracy between electronic health record users and potential for missing data. Most of these cohort studies did not report on baseline differences between feeding groups, with only Rosti et al. providing satisfactory evidence that the feeding groups were similar at study initiation.[30] Of the 4 quasi experimental studies, 2 did not confirm clear differentiation between the feeding groups, with some infants in HM groups consuming an appreciable amount of formula.[36,39]

All but 4 studies[19,27,29,39] exhibited risk for bias regarding sample size, power, or statistical analysis, although this is understandable considering the small population and rare outcomes under study (e.g., NEC). Ten studies had very small samples or low incidence of outcomes (e.g., NEC), and/or did not provide information on whether power was adequate for HM-related outcomes.[28,30–37,41] Five studies controlled for covariates,[27,28,30,39,40] but it was unclear whether 4 of these were powered for all outcomes.[28,29,39,40] For example, Blanco et al. reported sufficient power for the primary outcome of weight velocity, but was unclear as to the power for NEC outcomes.[40] Yu et al. completed a power analysis but did not control for covariates, and used potentially inappropriate tests for categorical variables with low frequency.[38] Becker et al., Boctor et al., and Combs and Marino reported large amounts of missing data[32] or lacked adequate description of analytical methods[31,34] which were significant limitations for results related to HM feeding.

Discussion

This review identified 16 articles that examined the impact of a HM diet in infants with CHD during the hospital stay. With the existing evidence, it is difficult to conclusively answer the primary research question regarding differences in outcomes between infants with CHD who receive HM, as compared to other types of feeding. The result with the highest level of certainty relates to the incidence of NEC. There is evidence that the incidence of NEC is lower in infants with CHD who are fed HM,[27,29,32] with Cognata et al.'s [27] well-designed retrospective cohort study and Blanco et al.'s [40] RCT both reporting significantly lower NEC with an exclusive HM diet. Both of these studies included modified Bell staging to determine diagnosis. In Lopez et al., infants with HLHS who developed NEC during the initial hospitalization and survived to stage 1 palliation discharge were less likely to be receiving any HM at discharge.[19] In this study, it should be noted that the type of feeding was reported at hospital discharge rather than before NEC development. While it is plausible that an infant's feeding plan at hospital discharge is reflective of nutrition received during the hospital stay, it is not certain that the infant received a 100% HM diet during the hospital stay. For example, not all hospitals utilize pasteurized donor HM as a bridge to MOM. In this case, an infant may be exposed to infant formula as the lactating parent is developing their milk supply. It is also possible that HM provision could have been negatively impacted by a complicated clinical course, lack of adequate support for the lactating parent in establishing milk supply, or provider or institutional preference – all of which could result in nutrition changes throughout the hospital stay. Thus, infants in Lopez et al.'s study may have been exposed to formula during their hospitalization, even if their feeding method at discharge was noted as 100% HM. Additionally, this study is a secondary analysis of the National Pediatric Cardiology Quality Improvement Collaborative registry, which includes approximately 60 cardiac centers across the United States. The authors note that criteria for NEC diagnosis was not standardized among institutions, which is a further limitation.

Overall, the findings in this review lend support to the hypothesis that HM is protective against NEC in infants with CHD. This is consistent with previous findings in the very low birthweight and preterm populations,[42,43] and reveals that a HM diet offers protection against this potentially devastating disease. However, there may be some concern that an exclusive HM diet could prevent NEC while resulting in slower growth. For example, Chowning et al. reported a dose-dependent relationship between exclusive HM feeding, decreased NEC, and decreased weight gain in very low birth weight neonates.[44] In the current review, only one study examined the impact of HM feeding on both NEC and growth outcomes.[40] Blanco et al. found that infants fed exclusive HM with HM-based fortifier demonstrated initial slower growth than infants fed bovine-based fortifier. [40] By day 30 of life, growth in the HM-based fortifier group exceeded that of the bovine-based fortifier group, and this trend continued through the end of the study – a result consistent with recent evidence on HM-based fortifier for preterm and very low birthweight infants.[45,46] Cognata et al. did not report growth outcomes; however, the focus of this study was on the development of NEC preoperatively, and most infants had surgery during the first two weeks of life (median 19.2 days for infants with ductal-dependent biventricular physiology, n = 119; 9.2 for all others, n = 427).[27] Considering the potential for clinical instability during the preoperative time, growth trends during the study period may not have been well established. While the results from Blanco et al. indicate that an exclusive HM diet with HM-based fortifier allows for both reduced risk for NEC and improved physical growth, future studies should investigate strategies to support growth with an exclusive HM diet when HM-based fortifier is not available.

Chylothorax

Chylothorax is another rare but serious complication of cardiac surgery, and treatment with a modified HM diet is a relatively new approach, with the first case study on this process published in 2004.[47] In the context of care for chylothorax, outcomes were generally not different between modified HM groups and infants receiving MCT formula. While Neumann et al. reported significantly fewer

treatment days for infants in a modified HM group, their results are skewed by one infant who received an MCT formula diet for 230 days.[37] Considering the small sample size of the MCT group (n = 10), the true difference between groups is likely much lower. Differences in other treatment outcomes (e.g., number of chest tube days, volume of chest tube drainage, length of stay) were not significant.

The impact of a modified HM diet on growth in the context of chylothorax was inconclusive. Kocel et al.[36] reported significant decreases in WAZ and LAZ from baseline, but included only 16 infants with a lack of definition between feeding groups. For example, infants in the modified HM group received as little as 45% modified HM, with the remainder supplemented by MCT formula.[36] Conversely, 3 (38%) infants in the MCT group required parenteral nutrition for between 5 and 19 days, compared to none in the modified HM group.[36] This variation in feeding practice highlights the difficulty of conducting feeding research in infants with CHD – particularly when examining a rare outcome, such as chylothorax. The remaining 3 studies found no significant differences in growth outcomes, although Di Lauro et al. caution that they did not recruit the most severely ill infants, who may have been at highest risk for growth failure.[39] Additionally, all studies examining the use of modified HM in chylothorax included small samples ($n \leq 35$), and it is possible that different groups may experience different results. Based on the available evidence, it appears that treatment of chylothorax with modified HM is a viable alternative to formula-based nutrition plans, with similar results related to chest tube volume and duration, treatment duration, length of stay, and growth. High-quality evidence including larger sample sizes is needed to clarify the impact of modified HM on outcomes related to chylothorax. It is also important to note that all 4 studies examining chylothorax outcomes in this review used a centrifuge to create low-fat HM,[28,36,37,39] with 1 of these providing parents with the option of portable centrifuges to use at home.[39] It is understandable that many hospitals in North America may not have the resources to implement centrifuge-based skim milk programs for chylothorax. Institutions would require a strong HM culture, along with financial and personnel resources to implement this type of program.[48] Other less expensive

methods of modifying HM for chylothorax treatment have been described.[49] Further testing of these methods in the CHD population is warranted, and should include qualitative methods to investigate any potential burden for families and hospital staff.

Weight gain

Impaired weight gain and physical growth can be a major concern for infants with CHD due to increased risk for poor surgical and developmental outcomes[4,5,50] and psychological stress for family caregivers.[6,7] It is difficult to compare growth outcomes between studies in this review, due to differences in feeding groups, outcome measures, and length of follow up. For example, 4 studies compared "breastfeeding" or "breast milk" groups with "formula," or "bottle" groups.[31,33,34,38] In 3 of these studies, infants in the breastfeeding groups were not required to receive exclusive HM.[31,33,34] Other studies examined HM feeding compared to standard or high-calorie formula,[30] predominant breastfeeding compared to mixed feeding or exclusive formula,[35] or HM-based fortifier compared to bovine-based fortifier.[40] Older studies may not reflect current practices regarding postoperative or interstage fortification. Anthropomorphic measures also varied among studies (e.g., average daily weight gain,[30,31,38,40] percentage of weight change,[34] WAZ[33,35]), and length of follow up ranged from the initial postoperative hospital stay[30,38] to the first year of life.[35]

Despite these limitations in study design, there appears to be some evidence that a well-managed HM diet may support improved weight gain for infants with CHD. Blanco et al.'s recent RCT reported that infants with SV CHD who received HM-based fortifier had greater weight velocity from birth to the end of the study than those on bovine fortifier.[40] Similar results have been found in other surgical congenital populations.[51] As Blanco et al.'s results were available only as a conference presentation, it was not clear whether the findings were adjusted to reflect the time that infants spent in the study, as length of participation varied due to infant clinical course. Full published results are needed to verify the strength of these findings. Additional studies supported increased growth for infants receiving HM, with

Yu et al. reporting significantly increased average weight gain for infants on exclusive HM diets,[38] while Combs and Marino found that infants in HM feeding groups tended to lose less weight at 5 months post discharge.[34] Both of these studies exhibit risk for bias related to design and analysis. While McCrary et al. reported that infants fed any HM tended to lose less weight at shunt palliation takedown surgery (at mean 5.6 ± 2.7 months), the authors cautioned that weight gain was insufficient for all infants in their cohort, and baseline differences between the HM and non-HM groups were not well described. The only study that demonstrated inferior weight-related outcomes for infants in HM feeding groups has serious design flaws (e.g., crossover between feeding groups; heterogeneous diagnoses and age groups; small sample; statistical analysis not well described) and does not reflect current practice.[31] The remaining studies revealed no significant differences in weight gain between infants receiving HM and those receiving other diets.[30,35] Taken as a whole, the results tentatively indicate that a well-managed HM diet – potentially including a HM-based fortifier when needed – may result in similar or improved weight-related outcomes for infants with CHD, although the evidence exhibits risk for bias. High-quality, carefully-designed studies are needed to fully understand the impact of HM feeding on weight gain and physical growth, so that best practices in managing a HM diet can be identified. Moreover, future research should investigate the impact of nutrition on the quality of growth outcomes for infants with CHD. Previous work in the preterm population reveals that infants fed with HM or direct breastfeeding experience slower initial weight gain, but ultimately better neurodevelopment[52] and recovery of body composition through fat-free mass deposition.[53] Infants with CHD are at risk for impaired neurodevelopment,[54] and inadequate growth has been shown to be associated with poor neurodevelopmental outcomes.[50] However, the relationship between nutrition type (e.g., MOM, pasteurized donor HM, formula, bovine or HM-based fortifier) and growth quality has not been examined in infants with CHD. The potential impact of HM feeding on neurodevelopment for these infants is an important direction for future research.

Other postoperative outcomes

The association between a HM diet and LOS was examined frequently, with 5 of 6 studies finding that infants in HM feeding groups had a shorter hospital LOS. The statistically significant result in Yu et al. should be interpreted with caution, as this study did not control for potential covariates (e.g., age, diagnosis, etc.).[38] Additionally, the authors note that infants in the formula feeding group often lived in rural areas, with parents who could not always travel to the surgical center. It is possible that this disparity in healthcare access could have delayed discharge or may have impacted outcomes in other unmeasured ways. Future studies with large sample sizes and robust analytical techniques should carefully examine the impact of HM on hospital LOS, as a reduction in LOS by even 1 day has clinical implications for lower hospital costs and benefit to families.

Yu et al. also reported differences in other postoperative feeding outcomes, with infants in the HM groups beginning enteral feeds earlier and achieving full feeds sooner.[38] Similar results in faster achievement of full feeds have been noted in some preterm populations.[55,56] For Yu et al., criteria for beginning enteral feeds included resumption of bowel sounds, typically on postoperative day 2–4, with feeds advanced based on gastric residuals. The authors present hypotheses for faster achievement of full feeds, but do not discuss potential reasons for earlier feeding readiness in the HM group, which could have been impacted by unmeasured covariates (e.g., variation in feeding based on individual clinician preference, level of family engagement/advocacy for feeding, etc.). Multisite studies with larger samples are needed to corroborate these findings, particularly as postoperative feeding practices are highly site- and provider-specific.[9] Yu et al., found additional benefits of HM feeding related to markers of nutritional status and incidence of complication.[38] Many of these analyses included low numbers and were likely not powered to detect true differences. Further evidence is needed to validate the results described in this study.

Definition of human milk feeding

Studies focused on HM feeding have been historically imprecise in defining what constitutes a HM feeding group.[57] The 16 studies in this review exhibit notable variation in delineating HM feeding, with 10 studies providing either no clear definition of HM feeding,[19,35,37,41] or allowing infants in HM groups to consume significant amounts of formula.[28,31,33,34,36,39] While it should be noted that examining HM feeding outcomes was not a primary aim of Becker and colleagues, this study assessed infant nutrition type on the day of NEC diagnosis, and assigned 5 (24%) infants to HM or formula feeding groups based on this data point.[32] The remaining 16 (76%) infants diagnosed with NEC were not included in the analysis due to missing feeding data on the day of diagnosis. The ambiguity in feeding group assignment in the studies under review complicates pooling of results and cross-study comparison. While there are ethical challenges inherent in researching HM feeding, it is difficult to make recommendations based on studies with multiple treatment interference, or with large amounts of missing data. Several recent studies addressed this problem by providing pasteurized donor HM for infants who were not able to receive 100% MOM,[27,29,40] although it should be noted that pasteurized donor HM is not an equivalent substitute for MOM.[58–60]

Future studies should explore HM dose response. Many studies in the current review allowed infants in a HM group to consume significant amounts of formula (e.g., range of up to 65% in Kocel et al.[36]), or considered a HM feeding group to include any amount of HM.[31–34] Kataria-Hale et al. hypothesize that their non-significant association between preoperative HM feeding and postoperative NEC may have been different if they had been able to calculate HM dose.[29] To our knowledge, no study has quantified the amount of HM received by infants with CHD or analyzed volume-associated differences in outcomes. Accurate methods to measure HM transferred via direct breastfeeding exist (e.g., test weighing),[61] and can be used to quantify volume for those infants who are not receiving exclusive expressed HM.

Harms

In the included studies, there were no harms associated with a HM diet. There is a need for well-designed, prospective research on the best ways to support long-term physical growth through a HM diet in this population, but the results in this group of studies indicate that a HM diet is not harmful to growth or development, and may in fact support physical growth. Given the well-documented nutritional, immunological, and relational benefits of a HM diet in both the healthy newborn population and in those needing neonatal ICU care,[43] the benefits of a well-managed HM diet outweigh any potential risks.

Clinical implications

Considering the evidence supporting decreased odds for preoperative NEC in infants with CHD who receive exclusive HM feeding, the possibility that a HM diet may decrease hospital LOS, the potential for improved postoperative feeding and nutrition outcomes, and the finding that a well-managed HM diet may support improved growth, we recommend that clinicians and healthcare systems make a concerted effort to support an exclusive HM diet, potentially fortified with HM-based fortifier when needed, for infants with CHD both during the hospital stay and after discharge. This aligns with global health organizations, which agree that HM is the preferred nutrition for both typically developing and vulnerable infants.[15,16,62] Clinicians should identify ways to support lactating parents in providing HM for their infant with CHD. Direct breastfeeding and HM expression are inherently challenging in the context of neonatal surgery and hospitalization,[11,63] and infants with CHD are at particular risk for early weaning from HM.[17,64] Furthermore, infants with CHD are often cared for at children's hospitals, potentially in a cardiovascular ICU. These institutional environments may not have a strong culture of prioritizing HM feeding and direct breastfeeding, in comparison to a birth hospital or a NICU. Previous research has demonstrated that parents of vulnerable infants born in a specialized birthing center inside a children's hospital were significantly more likely to initiate pumping and HM feeding for their infant with CHD, compared to infants born at an outside hospital.[65]

This systematic review could serve as a call to action for institutions caring for infants with CHD. First, healthcare providers in these facilities should examine their current lactation services and ensure that they are providing comprehensive, evidence-based lactation interventions during the antenatal period, through birth, during the infant's hospitalization, and post discharge. Second, healthcare institutions should examine their process of documenting enteral nutrition. Ideally, every enteral feed should be quantified to determine percentages of MOM, pasteurized donor HM, and infant formula so that percent exposure to HM could be calculated daily, weekly, and over the entire hospital stay. Third, hospitals caring for infants with CHD should consider investing in the necessary equipment and personnel to implement a skim milk program. For an infant with CHD, the early weeks of life are often a time of crucial interventions, intended to optimize growth and development throughout the lifespan. Support of HM feeding should be a key component of this early development plan, requiring a concerted interdisciplinary, family-centered approach including comprehensive, culturally-responsive lactation services that includes prenatal intervention, support for parental mental health, and evidence-based care.[66]

Directions for future research

The current review demonstrates that there are major gaps in the literature to be addressed through future research. The overall quality of the current evidence has limitations, with issues of statistical power and analysis affecting the group of studies. Additionally, studies used varying or unclear criteria for feeding group assignment, with infants in HM feeding groups often receiving significant amounts of non-HM nutrition for supplementation or fortification. While fortification may be necessary for some infants with CHD, future research should be clear about the percentage of non-HM feeding that is acceptable for an infant categorized in a HM study group. Ideally, improvements in enteral nutrition measurement and documentation would allow for studies to determine whether there are dose-response differences in outcomes between infants receiving HM, formula feeding, and/or bovine-based fortifier. While some recent studies exhibit more clarity in HM feeding group delineation,[27,39,40] this review

highlights the fact that CHD is inherently difficult to study. Physiological combinations of anomalies may be highly individualized, and two patients with the same diagnosis may experience very different clinical courses.[67] Research on nutrition for hospitalized infants with CHD is similarly complicated, as feeding plans can include various forms of nutrition and routes of nutrition delivery. It is challenging to tease apart the factors that interact to impact each infant's experience with CHD. Finally, clear standardization of outcome measurements would improve the quality of the evidence, particularly for rare diagnoses such as NEC and for growth-related outcomes.

Large, multisite studies implementing high-quality, adequately-powered prospective designs are needed to fully understand the impact of a HM diet on outcomes for infants with CHD, with robust statistical analysis that carefully controls for clinically-relevant covariates. These studies should aim to clarify the current inconclusive evidence, with a particular focus on outcomes related to growth and physical development. Growth failure is associated with increased morbidity and mortality in infants with CHD,[4,5] and a recent study highlighted the lack of evidence for best practices in managing growth with a HM diet in this population.[21] Therefore, future research should focus on exploring techniques for managing an infant's HM diet, which may include individualized fortification or separating the hindmilk of MOM.[68,69] Future work should focus on describing the longitudinal impact of a HM diet on physical growth and development, and should consider dose-dependent outcomes. Multisite studies can provide power to determine differences in rare outcomes such as NEC; however, standardization of outcome measurements among sites is a key consideration, and may be challenging to implement.

Of note, fewer than half of studies in this review reported race or ethnicity,[19,27–29,32,33,35] and only 3 offered any type of information on social or economic characteristics of the sample.[33,35,36] There may be unexplored social determinants of health (e.g., structural racism and structural inequity) or barriers to healthcare access (e.g., distance from center; language barriers) that could play a role in the relationship between infant nutrition and health outcomes.[70] For example, Yu et al. mention that many of the infants in

their formula feeding group came from rural families, who lived far from the tertiary hospital and could not travel to provide HM for their child.[38] This raises questions about differences in parental proximity or engagement that may have impacted health outcomes. Future studies should report social and familial information, and should interrogate the ways in which systems and institutions contribute to inequities in HM-associated outcomes for infants with CHD, particularly given that factors such as parental race, country of birth, level of education, neighborhood, socioeconomic status, and maternal parity have been shown to impact HM feeding and direct breastfeeding in other vulnerable neonatal populations.[71–73] Additionally, the impact of parental mental health on infant feeding and health outcomes cannot be ignored. Previous literature demonstrates the negative impact of emotional and physiological stress on HM production,[74,75] with higher levels of parental engagement and lower levels of anxiety and depression associated with improved HM outcomes.[76] Considering the potential for parental trauma in the context of a neonatal hospitalization, future work should adopt a holistic, culturally-responsive, family-centered approach to HM research that acknowledges infant feeding as an innate, nurturing parental act of care, as opposed to merely a medical intervention to be measured and documented.[77]

Strengths and limitations

The current review has several strengths. The search was conducted in multiple databases, with the assistance of an experienced health sciences research librarian. Reference lists were carefully examined for relevant publications. While non-English-language studies were excluded, a title review of non-English results identified no studies that appeared to meet the inclusion criteria. The review process included an in-depth methodological quality assessment by at least two independent reviewers, following the guidelines of validated critical appraisal tools.[26] Limitations include risk for bias in many studies; only 1 non-pilot RCT; a lack of information on social determinants of health and health inequities; and inconsistency in defining HM feeding among studies. The precise type of nutrition (e.g., MOM or donor HM) was often unclear. Sample sizes varied and many studies were not well powered, with subsequent

issues for statistical validity. While the review represents diverse CHD diagnoses, the exclusion criteria of several studies raises questions about the generalizability of the findings. For example, Yu et al.[38] report several significant results, yet include no infants with staged surgery for CHD, effectively eliminating infants that could be at the greatest risk for feeding-related morbidity and mortality. Similarly, DiLauro et al.[39] decided not to approach some unstable HM-fed infants undergoing treatment for chylothorax. Therefore, the results of this review may not fully describe the wide range of clinical experiences in the CHD population, with the sickest infants possibly underrepresented.

Conclusion

The current review included 16 studies reporting on the impact of a HM diet on outcomes for infants with CHD, as compared to other types of feeding. Based on assessment using the Joanna Briggs Critical Appraisal Tools,[26] the studies with the strongest evidence indicated that an exclusive HM diet reduces the odds of NEC in this population. Studies with higher risk for bias revealed that a HM diet may be associated with a shorter hospital LOS, improved postoperative feeding and nutritional outcomes, and improved growth. Therefore, given what is known about the conclusive benefits of HM diets in other populations (e.g., low birthweight and surgical infants) and the fact that this review identified some similar benefits for infants with CHD, we recommend that clinicians prioritize programs to improve HM feeding in infants with CHD. High-quality, multisite research on HM for infants with CHD is warranted, provided institutions have the appropriate resources and documentation. Larger studies with careful nutrition documentation and robust measures would allow for appropriate statistical power to provide more conclusive outcome data than is currently available.

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Chapter 3: Patterns of Breastfeeding and Human Milk Feeding in Infants with Single Ventricle Congenital Heart Disease: A Population Study of the NPC-QIC Registry (Manuscript #1)

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Abstract

Introduction: Infants with single ventricle congenital heart disease (SV CHD) undergo staged surgical and/or catheter-based palliation and commonly experience feeding challenges and poor growth. Little is known about human milk (HM) feeding or direct breastfeeding (BF) in this population.

Aim: To determine: (a) HM and BF prevalence for infants with SV CHD, and (b) whether BF at neonatal stage 1 palliation (S1P) discharge is associated with any HM at stage 2 palliation (S2P; ~4–6 months old).

Methods: Analysis of the National Pediatric Cardiology Quality Improvement Collaborative registry (2016–2021) using: (a) descriptive statistics for prevalence, and (b) logistic regression adjusted for multiple variables (e.g., prematurity, insurance, length of stay) to examine early BF/later HM feeding.

Results: Participants included 2491 infants from 68 sites. HM prevalence ranged from 49.3% any/41.5% exclusive before S1P to 37.1% any/7.0% exclusive at S2P. Direct BF ranged from 16.1% any/7.9% exclusive before S1P to 9.2% any/3.2% exclusive at S2P discharge. Prevalence varied among sites; e.g., 0%–100% any HM before S1P. Infants BF at S1P discharge had greater odds of any HM (OR=4.11, 95% CI=2.79–6.07, p<0.001) and exclusive HM (1.85, 1.03–3.30, p=0.039) at S2P.

Conclusions: The prevalence of HM and BF for infants with SV CHD was low and declined over time. Direct BF at S1P discharge was associated with increased odds of any HM at S2P. Wide variation suggests that site-specific practices impact feeding outcomes. HM and BF prevalence are suboptimal in this population, and identification of supportive institutional practices is needed.

Introduction

As the most common congenital anomaly, congenital heart disease (CHD) affects nearly 1 in 100 infants born in the United States (US).[1] Single ventricle (SV) CHD is considered the most critical CHD and requires three staged surgical and/or catheter-based palliations, with two occurring during infancy (i.e., neonatal stage 1; stage 2 at ~4–6 months of age). Recent guidelines[2] highlight the importance of human milk (HM) and direct breastfeeding (BF) in protecting against disease (e.g., necrotizing enterocolitis[3]) and developmental delay[4] in hospitalized infants. For infants with SV CHD, who experience substantial risk for these morbidities, HM and BF may be particularly essential.

However, little is known about HM and BF for infants with SV CHD. Previous studies[5–13] have reported generally low prevalence in a broad range of CHD diagnoses[5–7,12–14] or congenital anomalies[8–11] (e.g., 35% any HM at hospital discharge[8]) but typically include small samples from single centers. While these reports are informative, infants with SV CHD experience longer hospitalizations and more complications than those with biventricular and non-critical CHD diagnoses.[15] Furthermore, most studies do not distinguish between HM via any route and BF directly at the breast, despite the fact that direct BF improves cardiorespiratory stability during feeding for infants with CHD[16] and offers infant-specific immunological benefits.[17] Direct BF during neonatal hospitalization is associated with longer HM feeding duration for preterm infants,[18] but this association has not been examined in the CHD population.

We identified only two studies describing HM prevalence for infants with SV CHD. A multi-year Irish study[19] reported that, in 2018, 86% (n=18) of infants with SV CHD received predominant HM at stage 1 palliation (S1P) discharge. In contrast, a 2018 US study[20] found that only 15% (n=34) of infants with SV CHD received exclusive HM at S1P discharge. Neither of these studies was primarily focused on HM or reported direct BF.

To address the gap in knowledge about HM and BF for infants with SV CHD, we aimed to determine the prevalence of these practices at time points from birth through stage 2 palliation (S2P)

discharge and to test the hypothesis that direct BF at neonatal S1P discharge was associated with increased odds of HM feeding by any route at S2P. By analyzing a large, multisite SV CHD registry, this study offers foundational evidence by which to gauge future improvement in HM and BF for these vulnerable infants.

Methods

We analyzed the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) registry (2016–2021), which includes infants with SV CHD from >60 pediatric cardiology centers across the US. Parental informed consent or waiver was obtained by each site for enrollment in the registry, and data were entered online by site staff. The University of Minnesota Institutional Review Board approved this study and deemed it exempt from continuing review. Infants with SV CHD who completed S1P were included. Exclusion criteria included fetal/infant demise before S1P and family choice not to pursue postnatal treatment.

Feeding practices were measured: (a) preoperatively at S1P, (b) at S1P discharge, (c) at S2P; and (d) at S2P discharge, with registry measures in Table 3.1. At S2P discharge, only BF prevalence was assessable.

Definitions

We defined HM feeding as milk from a lactating person's breast, delivered via any route. The NPC-QIC registry does not differentiate between mother's own milk and donor HM. There were two HM outcomes: (a) any HM, in which an infant received exclusive HM or a combination of HM and formula; and (b) exclusive HM, in which an infant received only HM. Infant feedings were considered fortified if the recommended calorie density was ≥ 22 kcal/oz.

Direct BF was defined as HM directly from the breast. We use the term "breastfeeding" as it is the language in the NPC-QIC registry and acknowledge that individuals may prefer another term (e.g., chestfeeding[21]). The BF outcomes were: (a) any BF, in which an infant received exclusive BF or a

Table 3.1. Measures for Feeding Practices in the National Pediatric Cardiology Quality Improvement Collaborative Registry

Time point	Measure	Answer options	Answer type
1. Preoperatively at S1P	What type of enteral feedings did the patient receive prior to S1P (in addition to swab to the mouth)?	1. Breastfeeding 2. Bottle fed: Formula 3. Bottle fed: Human milk 4. Did not feed: Clinical reasons 5. Did not feed: Institutional practice not to feed patients prior to S1P 6. NG tube trophic 7. NG tube greater than trophic	Select all that apply
	What is the type of feeding via NG tube? (if applicable)	1. Breastmilk 2. Formula 3. Combination of breastmilk & formula	Select one
2. At S1P discharge	Route of nutrition recommended in the nutrition plan at discharge	1. G-tube/GJ tube 2. NG/NJ 3. Oral: Breastfed 4. Oral: Bottle fed	Select all that apply
	Type of nutrition recommended in the nutrition plan at discharge	1. Breastmilk 2. Formula 3. Combination of breastmilk & formula	Select one
	Calorie density recommended in the nutrition plan at discharge: (Kcal/oz)	Free entry (numeric, continuous)	Free entry
3. At S2P	Route of nutrition at S2P (preoperative)	1. G-tube/GJ tube 2. NG/NJ 3. Oral: Breastfed 4. Oral: Bottle fed 5. TPN (not feeding)	Select all that apply
	Type of nutrition utilized at S2P (preoperative)	1. Breastmilk 2. Formula 3. Combination of breastmilk & formula	Select one
4. At S2P discharge	Route of nutrition recommended in the nutrition plan at discharge	1. G-tube/GJ tube 2. NG/NJ 3. Oral: Breastfed 4. Oral: Bottle fed	Select all that apply

Abbreviations: G-tube = gastrostomy tube; GJ = gastrojejunostomy; NG = nasogastric; NJ = nasojejunal; S1P = stage 1 palliation; S2P = stage 2 palliation; TPN = total parenteral nutrition.

combination of BF and another type/route of nutrition; and (b) exclusive BF, in which an infant received only HM from the breast.

Covariates

Covariates for models were selected *a priori* based on factors associated with HM or BF in the

neonatal literature. These included prematurity, infant race,[22] Hispanic/Latino/a ethnicity, socioeconomic indicators[22] including social deprivation index[23] of residential zip code tabulation area (ZCTA) and insurance type, major genetic syndrome, postoperative complications, intubation duration, and S1P hospital length of stay.[8]

An infant was preterm if born <37 weeks gestational age. Response options for infant race included American Indian or Alaska Native, Asian, Black-African American, Native Hawaiian or other Pacific Islander, White, or other. Due to small numbers in some groups, response options were collapsed into Black-African American, White, or another race/multi-race. Insurance type response options were collapsed into government or private/self (i.e., commercial, non-US, or none/self). Residential zip codes were matched to ZCTAs and used to calculate an infant's social deprivation index,[23] an indicator of potential health inequities created from the American Community Survey (e.g., % in the ZCTA living in poverty; % <12 years education).

Data analysis

Analysis of prevalence. All analyses were conducted in R (versions 4.2.1/4.2.2). We calculated the valid percentage of feeding practices at each time point. Preoperative S1P prevalence was calculated in the entire sample and in the subgroup of infants who were enterally fed preoperatively. Prevalence at S2P was calculated in the full sample, in those who were discharged after S1P, and in those who remained hospitalized until S2P. We visually examined HM/BF patterns among NPC-QIC sites.

Missing data. Across the sample, 2.3% of data were missing. We conducted multiple imputation by chained equations using the *mice*[24] package, including variables listed in Appendix C and inspecting imputations for convergence and plausibility.[24]

Analysis of direct BF at S1P discharge and HM feeding at S2P. To determine whether direct BF at S1P discharge was associated with any or exclusive HM via any route at S2P, we fitted unadjusted and adjusted logistic regression models for each imputed data set, obtaining pooled estimates and 95%

confidence intervals (CIs) using the *mice* package. For sensitivity analyses, we conducted the same logistic regression analyses for the subset of infants receiving any HM at S1P discharge and in the complete case, unimputed data. We tested complete case models for multicollinearity by calculating the variance inflation factor (VIF) for each included variable. All VIF values were under 1.5, indicating no issues. Statistical significance was set at $p<0.05$.

Results

In 68 sites from the NPC-QIC registry, 92.5% (2491/2693) of infants met eligibility criteria. Characteristics of participants at baseline are in Table 3.2. The median (25th-75th%) infant age was 6 (4–8) days at S1P; 39 (28–59) days at S1P discharge; 144 (123–175) days at S2P; and 162 (139–193) days at S2P discharge.

Prevalence of HM feeding and direct BF

The prevalence of HM feeding and BF at all time points can be found in Table 3.3. Of the 57.8% of infants who were fed prior to S1P, 85.7% (95% CI: 83.9%–87.6%) received any HM and 27.8% (25.5%–30.1%) were directly BF. The prevalence of HM and BF declined over time, with 37.1% (34.6%–39.5%) of infants receiving any HM and 9.4% (8.0%–10.7%) BF at S2P. Infants who remained hospitalized between S1P and S2P had a slightly higher prevalence of HM at S2P than those discharged (39.5% vs. 36.7%), but lower BF prevalence (5.7% vs. 10.0%).

Variation in prevalence across NPC-QIC sites. Feeding practices varied widely across NPC-QIC sites (Figure 3.1). The prevalence of any HM ranged from 0–100.0% at both S1P time points and from 0–80.0% at S2P. The prevalence of any BF ranged from 0.0–57.8% preoperatively at S1P; 0.0–100.0% at S1P discharge; 0.0%–40.0% at S2P; and 0–44.4% at S2P discharge. Figure 3.2 is a visual representation of this variation stratified by site size (i.e., number of patients enrolled in the registry). While there were no substantial differences based on size, the largest sites (n>51 infants) appeared somewhat more likely to directly BF infants preoperatively. Figure 3.3 shows NPC-QIC sites with the top

Table 3.2. Baseline Characteristics of the Full Sample (N=2491)

	n (%)
Sex	
Female	988 (39.7)
Male	1501 (60.3)
Race	
Another Race/Multi-Race	297 (12.0)
Black/African American	397 (16.0)
White	1721 (70.0)
Hispanic or Latino/a ethnicity	
Yes	390 (16.4)
No	1987 (83.6)
Preterm (<37 weeks)	
Yes	307 (12.4)
No	2161 (87.6)
Primary cardiac diagnosis	
HLHS	1757 (70.5)
Other SV	734 (29.5)
Major genetic syndrome	
Yes	314 (12.6)
No	2177 (87.4)
Other major anomaly	
Yes	190 (7.6)
No	2301 (92.4)
Insurance type	
Government	1302 (54.6)
Private/Self	1084 (45.4)
RUCA of ZCTA	
Metropolitan	1971 (81.1)
Micropolitan	254 (10.5)
Rural	204 (8.4)
	mean (SD)
Birth weight (kg)	3.12 (0.61)
Median income of residential ZCTA	65,667 (23,849)
SDI score of residential ZCTA	51 (28)

Abbreviations: HLHS = hypoplastic left heart syndrome; kg = kilograms; RUCA = rural-urban commuting area; SD = standard deviation; SDI = social deprivation index; SV = single ventricle; ZCTA = zip code tabulation area.

Table 3.3. Prevalence of Human Milk Feeding and Direct Breastfeeding for Infants with Single Ventricle Congenital Heart Disease at Time Points from Birth Through Stage 2 Surgery Discharge

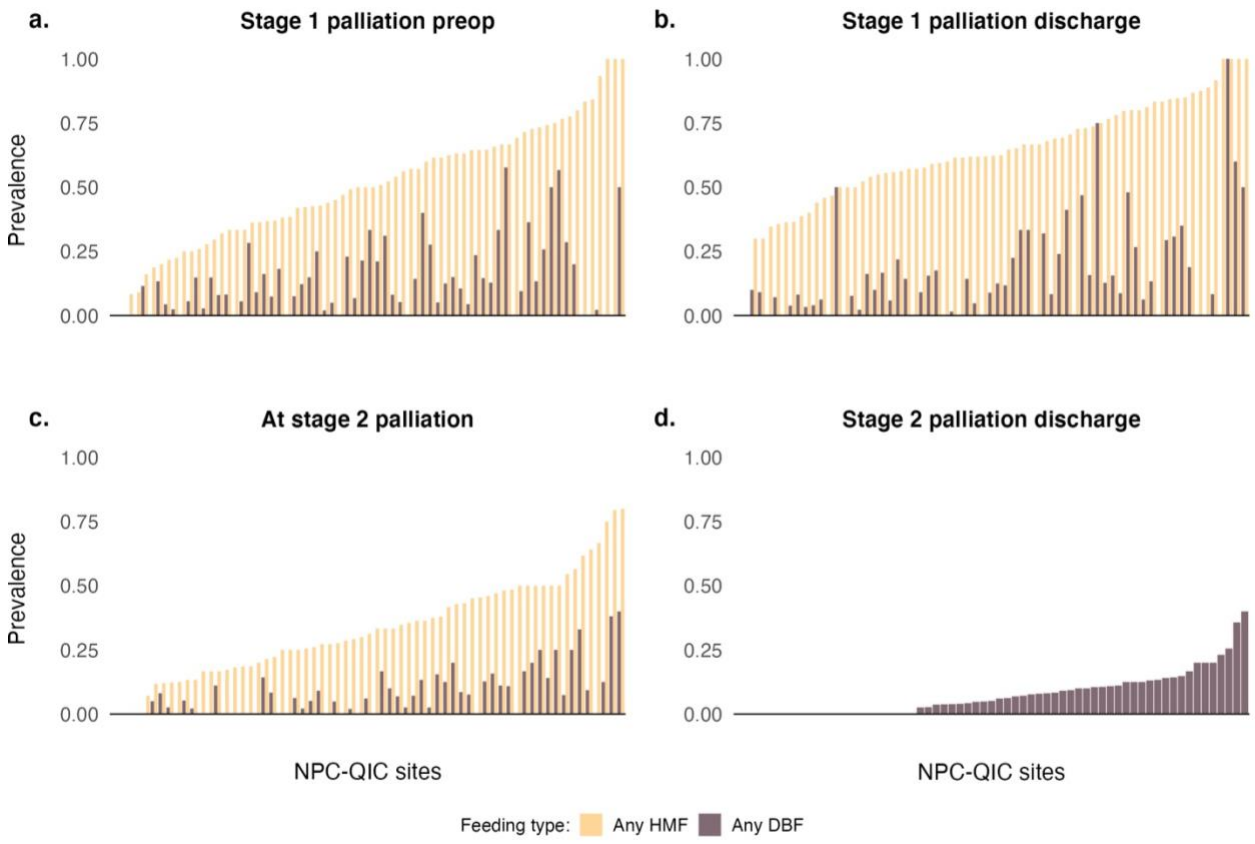
	Time point 1		Time point 2	Time point 3			Time point 4
	S1P preop[a] (all infants)	S1P preop (infants fed preop)[b]	S1P discharge[c]	S2P preop[d] (all infants)	S2P preop (discharged after S1P)	S2P preop (not discharged after S1P)	S2P discharge[e]
	N = 2491	N = 1440	N = 1946	N = 1849	N = 1584	N = 265	N = 1741
	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)
Human milk feeding							
Any	1220 (49.3) (47.3–51.3)	1220 (85.7) (83.9–87.6)	1229 (63.4) (61.3–65.6)	559 (37.1) (34.6–39.5)	471 (36.7) (34.0–39.3)	88 (39.5) (33.0–45.9)	–
Exclusive	1026 (41.5) (39.5–43.4)	1026 (73.0) (69.8–74.4)	181 (9.3) (8.0–10.6)	130 (7.0) (7.2–10.0)	118 (9.3) (7.6–10.8)	12 (5.6) (2.4–8.3)	–
None	1254 (50.7) (48.7–52.7)	203 (14.3) (12.4–16.1)	709 (36.6) (34.4–38.7)	949 (62.9) (60.5–65.4)	814 (63.3) (60.7–66.0)	135 (60.5) (54.1–67.0)	–
(Missing)	17	17	8	341	299	42	–
Direct breastfeeding							
Any	400 (16.1) (14.6–17.5)	400 (27.8) (25.5–30.1)	280 (14.4) (12.8–15.9)	173 (9.4) (8.0–10.7)	158 (10.0) (8.5–11.5)	15 (5.7) (2.9–8.4)	161 (9.2) (7.9–10.6)
Exclusive	197 (7.9) (6.9–9.0)	197 (13.7) (11.9–15.5)	30 (1.5) (1.0–2.1)	39 (2.1) (1.5–2.8)	38 (2.4) (1.7–3.2)	1 (0.4) (NC–1.1)	56 (3.2) (2.4–4.1)
None	2091 (83.9) (82.5–85.4)	1040 (72.2) (69.9–74.5)	1666 (85.6) (84.1–87.2)	1676 (90.6) (89.3–92.0)	1426 (90.0) (88.5–91.5)	250 (94.3) (91.6–97.1)	1580 (90.8) (89.4–92.1)
Fortification[f]							
Yes	–	–	1776 (92.8) (91.6–93.9)	–	–	–	–
No	–	–	138 (7.2) (6.1–8.4)	–	–	–	–
(Missing)	–	–	32	–	–	–	–

Abbreviations: CI = confidence interval; NC = not computable; preop = preoperative; S1P = stage 1 palliation; S2P = stage 2 palliation.

[a]Median (25th-75th%) age at surgery = 6 (4–8) days.
[b]A total of 1063 infants were not enterally fed preoperatively due to institutional policy or clinical reasons.
[c]Median (25th-75th%) age at S1P discharge = 39 (28-59) days (1.3 months).
[d]Median (25th-75th%) age at S2P = 144 (123–175) days (4.7 months).
[e]Median (25th-75th%) age at S2P discharge = 162 (139–193) days (5.3 months).
[f]Infants were considered to receive fortification if they had a recommended calorie goal of ≥ 22 kcal/oz.

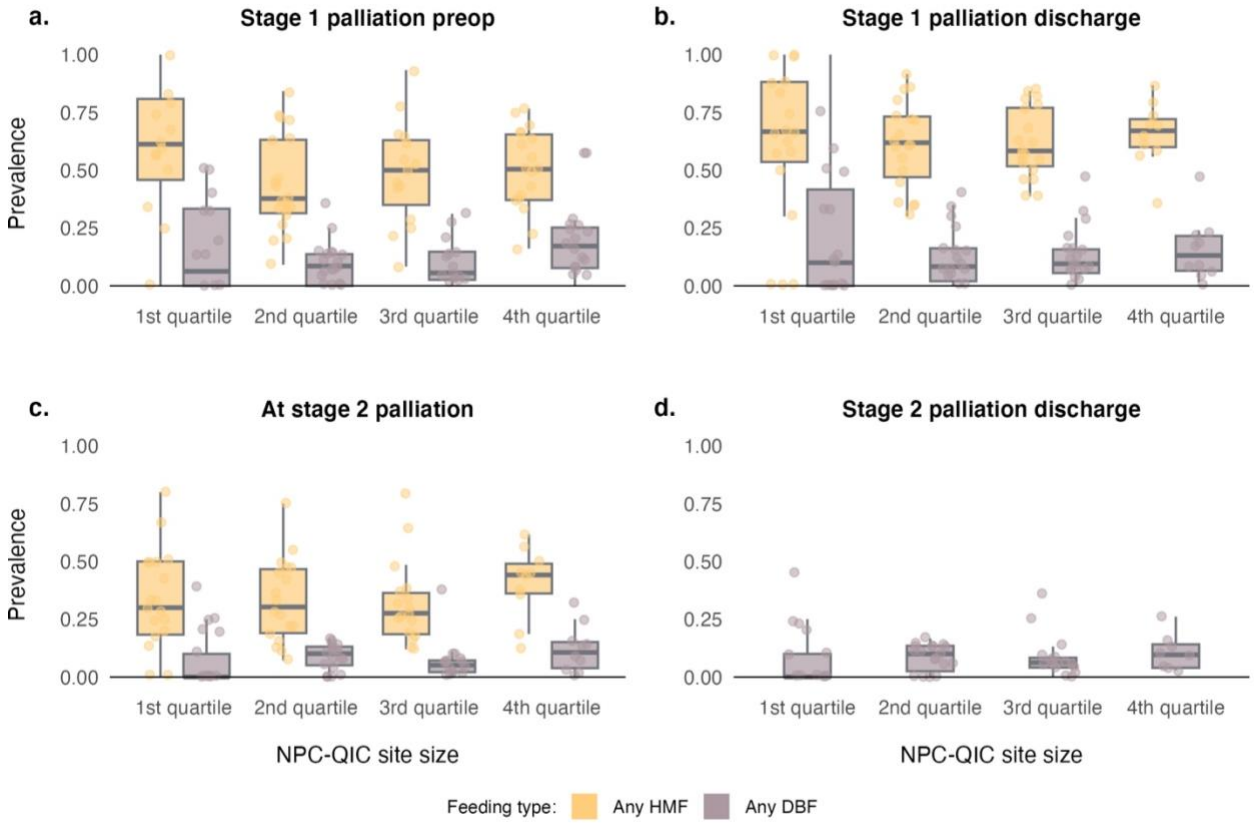
five highest prevalence of HM and BF at each time point. Due to potential for skewed results in small sites (e.g. a site with n=1 could have 0% or 100% prevalence), the 53 sites in the 2nd–4th size quartiles (all n>10) are presented. Site number 4 appeared most frequently as a top five HM/BF site. Other sites (i.e., 2, 10, 12, and 14) also appeared across multiple time points, indicating that certain sites have consistently strong HM/BF outcomes. There were no clear patterns of high prevalence related to site size.

Figure 3.1. Prevalence of Infants with Single Ventricle Congenital Heart Disease Receiving Any Human Milk and Any Direct Breastfeeding, Across NPC-QIC Sites (N=68)



Abbreviations: DBF = direct breastfeeding; HMF = human milk feeding; NPC-QIC = National Pediatric Cardiology Quality Improvement Collaborative.
Notes: Each column represents an NPC-QIC site. Human milk feeding and direct breastfeeding proportions are presented side by side for each site.
There were no human milk feeding data available for the stage 2 palliation discharge time point.

Figure 3.2. Median Prevalence of Any Human Milk Feeding and Any Direct Breastfeeding for Infants with Single Ventricle Congenital Heart Disease, by NPC-QIC Site Size (N=68)



Abbreviations: DBF = direct breastfeeding; HMF = human milk feeding; NPC-QIC = National Pediatric Cardiology Quality Improvement Collaborative.
Notes: Each quartile contains approximately the same number of sites, with 68 NPC-QIC sites represented. Quartile 1: n=0-10; quartile 2: n=11-28; quartile 3: n=29-51; quartile 4: n>51.
There were no human milk feeding data available for the stage 2 palliation discharge time point.

Figure 3.3. NPC-QIC Sites with the Top Five Highest Prevalence of Human Milk Feeding and Direct Breastfeeding for Infants with Single Ventricle Congenital Heart Disease at Each Time Point

Abbreviations: DBF = direct breastfeeding; HMF = human milk feeding; NPC-QIC = National Pediatric Cardiology Quality Improvement Collaborative; preop = preoperative.
Note: There were no human milk feeding data available for the stage 2 palliation discharge time point.

Association between direct BF at S1P discharge and HM feeding at S2P

A total of 1584 infants were discharged after S1P and underwent S2P. Sample characteristics of infants receiving any versus no HM at S2P are in Table 3.4. Analyses of associations between direct BF at S1P discharge and HM feeding at S2P can be found in Table 3.5. In both unadjusted and adjusted models, infants with any BF at S1P discharge had greater odds of HM at S2P, including 4.11 times greater adjusted odds of any HM (95% CI=2.79–6.07 greater, p<0.001) and 1.85 times greater adjusted odds of exclusive HM (1.03–3.30 greater, p=0.039).

Results of the sensitivity analyses can be found in Table 3.6. For the subset of infants receiving any HM at S1 discharge, direct BF was still associated with greater odds of any HM at S2P (2.86, 1.88–4.33, p<0.001). The results between models using imputed data and complete case models were similar in direction, with greater magnitude of effect size in complete case models.

Table 3.4. Sample Characteristics of Infants who Received Any Vs. No Human Milk at Stage 2 Palliation (Unimputed Data; N=1283)

	HM feeding at S2P n (%) or mean (SD)		
	Any (n = 471)	None (n = 812)	SMD[a]
Any direct BF at S1P discharge			0.69
Yes	154 (32.8)	56 (6.9)	
No	315 (67.2)	755 (93.1)	
Sex			0.01
Female	297 (63.1)	514 (63.3)	
Male	174 (36.9)	298 (36.7)	
Race			0.39
Another Race/Multi-race	50 (11.0)	97 (12.3)	
Black/African American	32 (7.1)	158 (20.0)	
White	371 (81.9)	534 (67.7)	
Hispanic or Latino/a ethnicity			0.05
Yes	63 (14.3)	126 (16.2)	
No	379 (85.7)	652 (83.8)	
Fetal diagnosis			0.16
Yes	422 (90.2)	687 (85.0)	
No	46 (9.8)	121 (15.0)	
Preterm (<37 weeks)			0.12
Yes	32 (6.9)	82 (10.2)	
No	434 (93.1)	725 (89.8)	

Born at the NPC-QIC center			0.14
Yes	288 (61.1)	439 (54.1)	
No	183 (38.9)	373 (45.9)	
Birth weight (kg)	3.25 (0.47)	3.16 (0.58)	0.17
Primary cardiac diagnosis			0.05
HLHS	335 (71.1)	596 (73.4)	
Other SV	136 (28.9)	216 (26.6)	
Major genetic syndrome			0.08
Yes	35 (7.4)	79 (9.7)	
No	436 (92.6)	733 (90.3)	
Other major anomaly			0.13
Yes	16 (3.4)	50 (6.2)	
No	455 (96.6)	762 (93.8)	
Insurance type			0.66
Government	137 (31.0)	488 (62.1)	
Private/Self	305 (69.0)	298 (37.9)	
Median income of residential ZCTA	72,100 (25,271)	62,983 (22,369)	0.38
SDI score of residential ZCTA	45 (28)	53 (28)	0.31
RUCA of ZCTA			0.06
Metropolitan	376 (81.2)	641 (80.8)	
Micropolitan	54 (11.7)	85 (10.7)	
Rural	33 (7.1)	67 (8.4)	
S1P preoperative feeding			0.02
Yes	283 (60.1)	497 (61.2)	
No	188 (39.9)	315 (38.8)	
S1P preoperative instability			0.18
Yes	163 (34.6)	354 (43.6)	
No	308 (65.4)	458 (56.4)	
S1P preoperative NEC			0.01
Yes	8 (1.7)	13 (1.6)	
No	463 (98.3)	799 (98.4)	
Age at S1P (days)	7 (10)	10 (15)	0.18
Weight at S1P (kg)	3.34 (0.51)	3.28 (0.55)	0.13
S1P type			0.11
Hybrid Norwood	18 (3.8)	49 (6.0)	
Norwood with BTT shunt	118 (25.1)	183 (22.5)	
Norwood with Sano	288 (61.1)	499 (61.5)	
Other	47 (10.0)	81 (10.0)	
S1P CPB time (minutes)	147 (57)	154 (57)	0.13
S1P cross clamp time (minutes)	72 (31)	71 (32)	0.04
S1P delayed sternal wound closure			0.10
Yes	345 (74.0)	562 (69.6)	
No	121 (26.0)	246 (30.4)	
S1P postop intubation duration (days)	7.0 (11.8)	7.1 (9.9)	0.00
S1P postop complications			0.14
Yes	303 (64.3)	577 (71.1)	
No	168 (35.7)	235 (28.9)	
S1P postop NEC			0.13
Yes	38 (8.1)	96 (11.8)	
No	433 (91.9)	716 (88.2)	

Weaned inotropes/vasoactive meds within 5 days postop			0.05
Yes	147 (31.2)	233 (28.7)	
No	324 (68.8)	579 (71.3)	
S1P postop days to enteral feeding	6.1 (17.4)	5.1 (8.2)	0.07
S1P postop days to full feeds	14 (13)	14 (12)	0.04
S1P length of stay (days)	41 (24)	49 (32)	0.27
# of cardiac meds at S1P discharge	2.22 (0.86)	2.22 (0.89)	0.00
Fortification at S1P discharge			0.05
Yes	419 (91.5)	737 (92.8)	
No	39 (8.5)	57 (7.2)	

Abbreviations: BF = breastfeeding; BTT= Blalock–Thomas–Taussig; CPB = cardiopulmonary bypass; HLHS = hypoplastic left heart syndrome; HM = human milk; kg = kilograms; meds = medications; NEC = necrotizing enterocolitis; NPC-QIC = National Pediatric Cardiology Quality Improvement Collaborative; postop = postoperative; preop = preoperative; RUCA = rural-urban commuting area; S1P = stage 1 palliation; S2P = stage 2 palliation; SD = standard deviation; SV = single ventricle; ZCTA = zip code tabulation area.
[a]SMD = absolute standardized mean difference; >0.10 indicates potential for substantial differences between groups.

Table 3.5. Associations Between Any Direct Breastfeeding at Stage 1 Surgery Discharge and Any or Exclusive Human Milk Feeding at Stage 2 Surgery for Infants with Single Ventricle Congenital Heart Disease in the NPC-QIC Registry (N=1584)

Variable	**OR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
	Unadjusted model: Any HM feeding			**Unadjusted model: Exclusive HM feeding**		
Any direct BF at S1P discharge	4.74	3.29–6.85	**<0.001**	2.17	1.25–3.78	**0.008**
	Adjusted model: Any HM feeding			**Adjusted model: Exclusive HM feeding**		
Any direct BF at S1P discharge	4.11	2.79–6.07	**<0.001**	1.85	1.03–3.30	**0.039**
Preterm (<37 weeks)	0.77	0.49–1.22	0.268	0.55	0.19–1.60	0.266
Race						
Another race/Multi-race	0.84	0.49–1.44	0.506	0.88	0.42–1.85	0.733
Black/African American	0.52	0.30–0.90	0.022	0.57	0.20–1.60	0.269
Hispanic/Latino/a ethnicity	1.02	0.67–1.57	0.908	0.84	0.46–1.53	0.568
Insurance type						
Government aid	0.46	0.34–0.63	<0.001	0.60	0.35–1.03	0.062
SDI score of residential ZCTA[a]	1.00	0.99–1.00	0.618	1.00	0.99–1.01	0.971
Major genetic syndrome	0.81	0.52–1.26	0.349	0.76	0.37–1.55	0.442
S1P postoperative complications[b]	0.89	0.68–1.15	0.364	0.94	0.64–1.37	0.737
S1P duration of intubation (days)	1.00	0.98–1.02	0.942	1.00	0.97–1.03	1.000
S1P length of stay (days)	1.00	0.99–1.00	0.683	1.00	0.99–1.01	0.588

Abbreviations: BF = breastfeeding; CI = confidence interval; HM = human milk; NPC-QIC = National Pediatric Cardiology Quality Improvement Collaborative; OR = odds ratio; S1P = stage 1 palliation; SDI = social deprivation index; ZCTA = zip code tabulation area.
Notes: Reference for race = White; reference for insurance type = private/self.
Analysis included pooled unadjusted and adjusted logistic regression using imputed data (m=10).
[a]SDI score = social deprivation index of the residential zip code tabulation area, an indicator of potential social health inequities (range, 0–100). A higher score indicates greater potential for social health inequities.
[b]S1P postoperative complications included arrhythmia requiring drug therapy or a pacemaker; necrotizing enterocolitis (treated medically or surgically); neurological deficit; paralyzed diaphragm; pleural effusion requiring drainage; pneumonia; pneumothorax requiring drainage or evacuation; respiratory insufficiency requiring reintubation; acute renal failure; seizure; sepsis; stroke; vocal cord dysfunction; or wound infection.

Table 3.6. Sensitivity Analyses of Associations Between Any Direct Breastfeeding at Stage 1 Surgery Discharge and Human Milk Feeding at Stage 2 Surgery for Infants with Single Ventricle Congenital Heart Disease in the NPC-QIC Registry

Variable	OR	95% CI	p value
Sensitivity analysis[a] including the subset of infants who were receiving any HM feeding at S1P discharge			
Any HMF			
Any direct BF at S1P discharge (unadjusted)	2.84	1.91–4.20	<**0.001**
Any direct BF at S1P discharge (adjusted)[b]	2.86	1.88–4.33	<**0.001**
Exclusive HM feeding			
Any direct BF at S1P discharge (unadjusted)	1.69	0.98–2.90	0.057
Any direct BF at S1P discharge (adjusted)[b]	1.61	0.92–2.81	0.093
Sensitivity analysis[c] using complete case, unimputed data			
Any HMF			
Any direct BF at S1P discharge (unadjusted)	6.64	4.79–9.33	<**0.001**
Any direct BF at S1P discharge (adjusted)[b]	6.30	4.27–9.43	<**0.001**
Exclusive HM feeding			
Any direct BF at S1P discharge (unadjusted)	3.34	2.18–5.05	<**0.001**
Any direct BF at S1P discharge (adjusted)[b]	2.37	1.45–3.82	<**0.001**

Abbreviations: BF = breastfeeding; CI = confidence interval; HM = human milk; NPC-QIC = National Pediatric Cardiology Quality Improvement Collaborative; OR = odds ratio; S1P = stage 1 palliation.
[a]Analysis included pooled logistic regression using imputed data.
[b]Adjusted for prematurity, infant race, Hispanic/Latino/a ethnicity, socioeconomic indicators including insurance type and social deprivation index of residential zip code tabulation area, diagnosis of a major syndrome, clinical complications postoperatively, duration of intubation, and stage 1 surgery hospital length of stay.
[c]Analysis included logistic regression using generalized linear regression models for complete case data.

Discussion

To our knowledge, this is the first broadscale examination of HM and BF in the SV CHD population, the first to investigate direct BF for these infants, and the largest study of HM/BF for infants with any form of CHD. Of great importance is that BF at neonatal S1P discharge was associated with increased odds of HM by any route at S2P.

Prevalence of HM feeding and direct BF

In our sample, the prevalence of HM and BF for infants with SV CHD was lower than recommended,[25] lower than the US population average (i.e., 55.8% any/24.9% exclusive HM at 6 months old),[26] and declined over time. These findings are consistent with previous reports of low HM and BF

prevalence for infants with CHD.

Stage 1 palliation preoperative HM and direct BF prevalence. For infants who were preoperatively fed in our sample, the prevalence of any HM prior to S1P was 85.7% with 73.0% receiving exclusive HM. This prevalence is in line with current US rates of 83.2% postnatal HM feeding initiation,[26] suggesting that lactating parents of infants with SV CHD have similar infant feeding goals as parents of infants who are born healthy. In comparison, a 2019 US single-site study[27] found that 54.5% of preoperatively-fed infants with various CHD diagnoses received exclusive HM. Interestingly, a 2021 study[28] at the same institution revealed that the subsequent implementation of a preoperative feeding protocol resulted in 100% exclusive preoperative HM, underscoring the key role of institutional practices in feeding these hospitalized infants.

Only 27.8% of preoperatively-fed infants in our sample directly BF prior to S1P. To our knowledge, the only previous report on the topic is a 2004 study,[14] with 44% of infants (n=30) BF before neonatal surgery for various CHD diagnoses. This 2004 study was conducted at a site that had implemented a system-wide lactation support program, with results representing an increase from 14% postnatal direct BF initiation before this institutional change. The comparatively lower BF rate in our study substantiates recent qualitative work[29] in which lactating parents of infants with critical CHD from 26 US cardiac centers explained that, while HM expression was typically supported, direct BF was often discouraged during the neonatal hospitalization. Direct BF as the first method of oral feeding benefits other hospitalized neonatal populations (e.g., increased HM at discharge,[30] shorter length of stay,[30] improved parental satisfaction with care[29,31]). While some infants with SV CHD are not physiologically able to eat by mouth, future work is needed to identify interventions to increase the prevalence of BF for infants who can be orally fed during the S1P preoperative time.

Approximately half of the infants in our sample did not receive preoperative enteral feedings due to clinical reasons or institutional policy. When considering all infants in our sample, the prevalence of

HM feeding during the early days of life was much lower than the US average, at 49.3%. This is concerning, as delayed HM feeding and direct BF may negatively impact immune development[32] and the gut microbiome.[33] Considering that the SV CHD population is at risk for serious complications such as necrotizing enterocolitis,[34] this low prevalence of preoperative HM and BF warrants further attention.

Stage 1 hospital discharge HM prevalence. At S1P hospital discharge, 63.4% of infants received any HM, with only 9.3% fed exclusive HM. Previous reports of HM feeding at neonatal cardiac surgery discharge vary.[8,11,19] A 2021 US study[8] described 35% any HM and 21% exclusive HM at discharge in a small number of infants with CHD (n=37). A 2021 study[11] from Brazil including 22 infants with cardiac anomalies reported 77.3% any HM and 36.4% exclusive HM at discharge. However, the diagnoses in this study were not reported and, as length of stay ranged from 3–66 days, it is unlikely that all infants underwent intervention. A 2022 Irish study[19] (n=90) reported an increase in HM for infants with SV CHD at S1P discharge over time (i.e., 24% predominant HM in 2014 to 86% in 2018) due to a system-wide quality improvement project. The prevalence of any HM at S1P discharge in our study falls between these reports; however, exclusive HM prevalence was lower in our sample than has been described, possibly due to widespread fortification practices.

Human milk prevalence at S2P. After S1P discharge the prevalence of HM for infants with SV CHD dropped below the US average, which is consistent with previous studies of infants with all CHD diagnoses.[7,12] A 2020 Brazilian study[7] reported 40.7% any/15.7% exclusive HM at 6 months old but included infants with CHDs that may not have required intervention. Our findings of 37.1% any/7.0% exclusive HM at S2P (median age, 4.7 months) are lower at an earlier time point, but slightly higher than Shine et al.'s[19] Irish study, in which 30% of infants with SV CHD received all/partial HM at S2P. In contrast, a 2010 Norwegian national survey[6] found that 74% of infants with moderate–severe CHD received at least some HM at 6 months. This substantially higher rate could reflect comprehensive national BF support and high population HM feeding.[35] The disparity in prevalence between this

Norwegian cohort and our sample points to socioecological factors as contributors to the suboptimal HM prevalence in our study.

Direct BF prevalence post S1P. In our sample, the low number of infants BF prior to S1P declined quickly, with only 14.4% of infants BF at S1P discharge (median 1.3 months old) and 9.2% at S2P discharge (median 5.3 months old). Exclusive BF prevalence was extremely low across all time points. It is difficult to compare our results to previous studies, as there are few reports of direct BF for infants with CHD. Torowicz et al.'s[5] 2015 US study reported that, for infants hospitalized for CHD and receiving HM, 13% of feeds occurred via direct BF. Spence et al.'s[12] 2011 Australian study found that, while almost 68% of infants with CHD were BF at hospital discharge, this number dropped to ~30% at 6 months; however, only 59% of infants in this study underwent neonatal open-heart surgery with cardiopulmonary bypass.[12] Our results echo qualitative reports that direct BF in this population is not often prioritized by healthcare teams and institutions,[29,36] and may be complicated by lengthy fortification and an exclusive concern about weight gain as the important outcome variable.[29]

Variation among sites. We found that HM and BF prevalence varied widely among NPC-QIC sites, which is unsurprising given the documented variation in clinical feeding practice for infants with SV CHD.[37] Our findings suggest that site-specific practices have a substantial impact on feeding outcomes, which aligns with previous research identifying institutional culture and policy as key to HM and BF.[28,31,38] Interventions to increase HM/BF prevalence in hospitalized neonates have been described[2,31,39] (e.g., pre- and postnatal condition-specific lactation counseling; sustained skin-to-skin contact; direct BF as the first oral feed; specialized staff training), but these interventions have not been applied across settings. A cohesive, institution-wide approach to lactation support is particularly important for infants with SV CHD, whose feeding practices are heavily monitored by various teams throughout the first year of life.[29] The variation in HM feeding and BF in our sample indicates that there is substantial room for population-level improvement, despite clinical challenges inherent to this

population.

Interestingly, there did not appear to be consistent differences in HM and BF prevalence based on NPC-QIC site size. Associations between high-volume institutions and outcomes such as length of stay and postoperative complications have been demonstrated,[15] and it is plausible that larger institutions could have specialized lactation, speech, and feeding support; access to pasteurized donor HM; and experience supporting HM/BF. Alternatively, larger sites may care for high-risk infants who could be less likely to feed preoperatively. While the top-performing site in our sample was in the largest size quartile, other sites with consistently strong HM and BF prevalence varied in size.

Association between direct BF at S1P discharge and HM feeding at S2P

We found that direct BF at S1P discharge was a significant predictor of HM feeding by any route at S2P – an association that has not been previously demonstrated for infants with CHD. Our results are consistent with qualitative accounts highlighting the burden of extended milk expression[29] and with research in preterm populations.[18] These findings underscore the critical need to improve institutional support not only for HM, but also for direct BF during neonatal hospitalization for SV CHD. For these infants, who experience risk factors for necrotizing enterocolitis, infection, and neurodevelopmental delay throughout the first year of life, increased duration of exposure to the protective benefits of HM may be particularly important in optimizing health. Moreover, for many lactating parents, direct BF is deeply meaningful in ways that extend beyond nutritional and immunological concerns.[29] For these parents, institutional support of BF goals is a crucial component of care.[29] Unfortunately, a recent study[29] revealed that few US institutions or providers prioritized direct BF for infants hospitalized for CHD, with many actively discouraging the practice. A consequent breakdown in trust resulted in some parents going against feeding recommendations in order to protect the BF relationship with their child.[29] The lack of support for parental feeding goals often exacerbated parents' psychological distress at a highly traumatic time[29] and is in opposition to individualized, family-centered, developmental care.[40]

Future research is needed to identify factors that support or limit HM and BF for infants with SV CHD, thus highlighting modifiable targets for improvement. Given the variation identified in this study, investigation of institutional factors that contribute to above-average HM and BF prevalence is warranted. There is an urgent need for translational research and quality improvement to develop clinically-appropriate, family-centered interventions particularly focused on the S1P hospitalization, to improve the low prevalence of HM and BF for these vulnerable infants.

Strengths and limitations

Our findings address limitations of the current evidence by focusing specifically on SV CHD; examining prevalence over time in a large, multisite sample; and distinguishing between HM feeding and direct BF. Limitations include those inherent to analysis of a national registry, including possibly inaccurate, inconsistent, or missing data. It was not possible to determine which infants were physiologically incapable of direct BF. Additionally, no information was available on dose or frequency of HM and BF. It is unclear whether BF included non-nutritive practice at the breast, and oral care with HM – a common practice – was not reported. We were unable to determine whether infants fed HM received mother's own milk, donor HM, or a combination. Lastly, data on feeding practices at S1P discharge were based on the route/type of nutrition recommended by providers, but actual feeding practices by family caregivers may have differed.

Conclusion

In this study of a large national registry, the prevalence of HM and direct BF for infants with SV CHD was low and declined over time. Direct BF at neonatal S1P discharge was associated with increased odds of HM feeding by any route at the subsequent S2P. Wide variation across NPC-QIC sites suggests that site-specific practices impact feeding outcomes. HM and BF prevalence are suboptimal in this population, and future research is needed to identify factors that support or limit these feeding practices for infants with SV CHD. Evidence-based, family-centered interventions adapted for the physiological

needs of this unique population are warranted. Direct BF before S1P discharge appears to be an important intervention to improve HM duration. HM/BF research is urgently needed to facilitate parental feeding goals and optimize the health of these vulnerable infants.

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Chapter 4: Predictors of Human Milk Feeding and Direct Breastfeeding for Infants with Single Ventricle Congenital Heart Disease: Machine Learning Analysis of the National Pediatric Cardiology Quality Improvement Collaborative Registry (Manuscript #2)

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Abstract

Objective: To identify factors that support or limit human milk (HM) feeding and direct breastfeeding (BF) for infants with single ventricle (SV) congenital heart disease (CHD) at neonatal stage 1 palliation (S1P) discharge and at stage 2 palliation (S2P) (~4–6 months old). These factors are currently unknown.

Study Design: Analysis of the National Pediatric Cardiology Quality Improvement Collaborative registry (2016–2021; 67 sites). Primary outcomes were any HM, exclusive HM, and any direct BF at S1P discharge and at S2P. The main analysis involved multiple phases of elastic net logistic regression on imputed data to identify important predictors.

Results: For 1944 infants, the strongest predictor domain areas included preoperative feeding, demographics/social determinants of health (SDoH), feeding route, clinical course, and site. Significant examples include: Preoperative BF was associated with any HM at S1P discharge (OR=2.02, 95% CI=1.74–3.44) and any BF at S2P (2.29, 1.38–3.80); Private/self insurance was associated with any HM at S1P discharge (1.91, 1.58–2.47); Black/African American infants had lower odds of any HM at S1P discharge (0.54, 0.38–0.65) and at S2P (0.57, 0.30–0.86). Adjusted odds of HM/BF practices varied among NPC-QIC sites.

Conclusions: Preoperative feeding practices predict later HM and BF for infants with SV CHD; therefore, family-centered interventions focused on HM/BF during the S1P preoperative time are needed. These interventions should include evidence-based strategies to address implicit bias and racism and seek to minimize disparities related to SDoH. Future research is needed to identify supportive practices common to high-performing NPC-QIC sites.

Introduction

Infants with single ventricle (SV) congenital heart disease (CHD) experience low rates of human milk (HM) feeding and direct breastfeeding (BF). While individual institutions may vary, a recent United States (US)-based, 5-year population analysis of 2491 infants with SV CHD reported a prevalence of only 7% exclusive HM and 9.4% any BF at approximately 5 months old.[1] These critically-ill infants typically require three palliative surgeries and/or catheter-based interventions, including a high-risk neonatal stage 1 palliation (S1P) followed by stage 2 palliation (S2P) at ~4–6 months old. Infants with SV CHD are at risk for complications including necrotizing enterocolitis,[2] hospital-acquired infection,[3] feeding intolerance,[4] and neurodevelopmental delay.[5] Given that HM feeding and BF are associated with reduced incidence of these complications in preterm and other surgical congenital populations,[6–9] increasing the prevalence of HM/BF for infants with SV CHD has the potential to improve the health of these vulnerable infants.

Evidence focused on HM and BF in the context of CHD is limited,[10] however, and only three studies focus specifically on HM/BF for infants with SV physiology.[1,11,12] No previous research has identified factors that support or limit HM/BF for infants with any form of CHD. While factors associated with HM/BF for preterm populations have been described,[13–15] this evidence may not fully capture the unique challenges related to SV CHD (eg, neonatal surgery, extensive time *nil per os* (npo; ie, nothing by mouth), volume restriction, lengthy fortification, impaired mesenteric circulation, historic discouragement of direct BF).[16–19]

Thus, the aim of this study was to identify factors that support or limit HM and direct BF for infants with SV CHD at S1P discharge and at S2P (ie, at the time of the stage 2 palliative surgery or intervention). Based on a 2022 systematic review on risk factors for oral feeding problems in infants with CHD,[20] we hypothesized that variables related to diagnosis, clinical course, preoperative feeding practices, and clinical site would be associated with HM/BF practices in the SV CHD population.

Additionally, demographic factors, social determinants of health (SDoH), and disparities in healthcare access have been shown to impact HM/BF for term and preterm infants,[13,14,21,22] but reporting of these variables has been strikingly neglected in CHD feeding research.[20] Identification of supportive and limiting factors could highlight modifiable targets for improvement and inform the development of culturally-responsive, family-centered interventions to address the low prevalence of HM and BF in this population, with the potential to improve the health of infants with SV CHD.

Methods

We conducted a retrospective cohort analysis of the US-based National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) registry (2016–2021), which includes >2500 infants with SV CHD from >60 sites ranging in size from 1– >150 infants. We included infants who were discharged after completing S1P, and excluded infants remaining inpatient until S2P as they were missing necessary S1P discharge data. Parental informed consent or waiver of consent for registry enrollment was obtained per site. The University of Minnesota Institutional Review Board approved this study and deemed it exempt.

Infant feeding outcomes

We used previously described definitions of HM feeding and direct BF.[1] Briefly, HM feeding included lactating parent/mother's own milk (MOM) or donor HM via any route, while direct BF included HM directly from a lactating person. The NPC-QIC registry does not record oral care with HM (ie, HM applied to the infant's mouth while npo; immunotherapy) and does not differentiate between MOM and pasteurized donor HM. The NPC-QIC registry uses the term "breastfeeding," and we acknowledge that other terminology (eg, chestfeeding) may be preferred.[23] Outcomes of interest were any HM (ie, exclusive HM or a combination of HM/formula via any route); exclusive HM; and any BF. Registry feeding measures at S1P discharge and at S2P have been previously described.[1]

Predictor variables

Analyses were conducted in R (version 4.2.1/4.2.2).[24] Selection of numerous potential predictor variables was informed by the literature[13,14,20,21] (see Table 4.1, column 1). We calculated weight-for-age and length-for-age z-scores for term and preterm infants using the *peditools* package.[25] We used infants' residential zip codes to create variables related to SDoH, including the rural-urban commuting area (RUCA) code[26]; the median income of each infant's crosswalked[27] zip code tabulation area (ZCTA) via the *tidycensus* package;[28] and the social deprivation index (SDI) score,[29] which is a validated indicator of a ZCTA's relative level of deprivation created from demographic characteristics of the American Community Survey. Additional strategies for variable transformation of prematurity, infant race, and insurance type have been previously described.[1]

Statistical analysis

At each time point, we initially compared infants who achieved each feeding outcome with those who did not by calculating the standardized mean difference (SMD) for each covariate.[30] Across the sample, 1.2% of data were missing. We applied multiple imputation by chained equations (m=10) using the *mice* package,[31] including all potential predictor and outcome variables.[31]

Elastic net logistic regression. We screened for key predictors by conducting elastic net logistic regression for each feeding outcome at each time point on each imputed data set (ie, 10 regressions for each outcome at each time point), using the *caret*[32] and *glmnet*[33] packages. Elastic net regression offers advantages over traditional regression methods. By using regularization to reduce overfitting and shrink coefficients toward 0, the elastic net approach is useful for sparse variable selection with good accuracy in the context of multiple predictors.[34] Elastic net regression handles collinearity better than other regularization techniques (eg, LASSO), as the elastic net tends to group and include important collinear variables rather than eliminating one arbitrarily.[34]

For each imputation, the data were split into training (80%) and testing (20%) sets. The model was trained using 10-fold cross validation to set tuning parameters. Estimates and weighted variable

Table 4.1. Individual, Clinical, and Surgical Factors of Infants in the NPC-QIC Registry Compared by Human Milk Feeding and Direct Breastfeeding Practices at Stage 1 Palliation Discharge (n = 1944) and at Stage 2 Palliation (n = 1578)

	At stage 1 palliation discharge n (%) or mean (SD)								
	Any human milk feeding			Exclusive human milk feeding			Direct breastfeeding		
	Any n = 1229	None n = 707	SMD	Exclusive n = 181	Not exclusive n = 1754	SMD	Any n = 280	None n = 1664	SMD
Prenatal variables									
Fetal diagnosis			0.14			0.19			0.13
Yes	1079 (65.0)	582 (35.0)		166 (10.0)	1494 (90.0)		249 (14.9)	1420 (85.1)	
No	146 (55.1)	119 (44.9)		15 (5.7)	250 (94.3)		28 (10.6)	237 (89.4)	
Characteristics at birth									
Birth year			0.06			0.26			0.11
2016	100 (59.5)	68 (40.5)		27 (16.2)	140 (83.8)		27 (16.0)	142 (84.0)	
2017	219 (63.7)	125 (36.3)		36 (10.5)	308 (89.5)		43 (12.5)	302 (87.5)	
2018	246 (62.8)	146 (37.2)		31 (7.9)	361 (92.1)		62 (15.8)	331 (84.2)	
2019	277 (63.5)	159 (36.5)		34 (7.8)	402 (92.2)		57 (13.0)	381 (87.0)	
2020	273 (65.2)	146 (34.8)		34 (8.1)	385 (91.9)		65 (15.4)	356 (84.6)	
2021	114 (64.4)	63 (35.6)		19 (10.7)	158 (89.3)		26 (14.6)	152 (85.4)	
Born at the NPC-QIC center			0.02			0.07			0.10
Yes	703 (64.0)	396 (36.0)		97 (8.8)	1001 (91.2)		170 (15.4)	932 (84.6)	
No	526 (62.8)	311 (37.2)		84 (10.0)	753 (90.0)		110 (13.1)	732 (86.9)	
Preterm (<37 weeks)			0.23			0.24			0.16
Yes	93 (47.2)	104 (52.8)		9 (4.6)	189 (95.9)		18 (9.1)	179 (90.9)	
No	1127 (65.5)	593 (34.5)		172 (10.0)	1547 (90.0)		260 (15.0)	1468 (85.0)	
WAZ at birth	-0.09 (1.12)	-0.24 (1.03)	0.14	-0.14 (0.95)	-0.14 (1.11)	-0.01	0.02 (0.85)	-0.17 (1.13)	0.19
Primary cardiac diagnosis			0.07			0.03			0.13
HLHS	127 (58.8)	89 (41.2)		136 (10.1)	1215 (89.9)		206 (15.2)	1151 (84.8)	
Other SV	1102 (64.1)	618 (35.9)		45 (7.7)	539 (92.3)		74 (12.6)	513 (87.4)	

Major genetic syndrome			0.12			0.12			0.15
Yes	60 (52.2)	55 (47.8)		22 (10.2)	194 (89.8)		22 (10.2)	194 (89.8)	
No	1169 (64.2)	652 (35.8)		159 (9.2)	1560 (90.8)		258 (14.9)	1470 (85.1)	
Other major anomaly			0.14			0.13			0.10
Yes	887 (65.7)	464 (34.3)		16 (13.9)	99 (86.1)		9 (7.8)	106 (92.2)	
No	342 (58.5)	243 (41.5)		165 (9.1)	1655 (90.9)		271 (14.8)	1558 (85.2)	
Sex			0.05			0.01			0.12
Female	470 (61.9)	289 (38.1)		70 (9.2)	688 (90.8)		96 (12.6)	667 (87.4)	
Male	759 (64.5)	418 (35.5)		111 (9.4)	1066 (90.6)		184 (15.6)	997 (84.4)	
Race			0.40			0.26			0.21
Another race/Multi-race	147 (65.9)	76 (34.1)		12 (5.4)	211 (94.6)		30 (13.5)	193 (86.5)	
Black/African American	123 (41.3)	175 (58.7)		20 (6.7)	278 (93.3)		26 (8.7)	273 (91.3)	
White	918 (67.4)	445 (32.6)		145 (10.6)	1217 (89.4)		209 (15.3)	1161 (84.7)	
Hispanic or Latino/a ethnicity			0.05			0.20			0.02
Yes	181 (60.1)	120 (39.9)		18 (6.0)	283 (94.0)		41 (13.5)	262 (86.5)	
No	988 (63.6)	565 (36.4)		161 (10.4)	1391 (89.6)		219 (14.0)	1340 (86.0)	
Insurance type			0.53			0.34			0.37
Government	515 (52.1)	473 (47.9)		67 (6.8)	921 (93.2)		98 (9.9)	894 (90.1)	
Private/Self	666 (75.7)	214 (24.3)		110 (12.5)	769 (87.5)		164 (18.6)	719 (81.4)	
Median income of residential ZCTA	69,108 (25,019)	60,223 (20,771)	0.39	68,060 (23,156)	65,655 (24,025)	-0.10	74,678 (25,346)	64,373 (23,342)	0.42
SDI score of residential ZCTA[a]	47 (28)	56 (27)	-0.32	45 (27)	51 (28)	0.22	43 (28)	52 (28)	-0.31
Rural-urban commuting area			0.11			0.08			0.19
Metropolitan	995 (64.8)	540 (35.2)		146 (9.5)	1388 (90.5)		238 (15.4)	1303 (84.6)	
Micropolitan	113 (57.9)	82 (42.1)		15 (7.7)	180 (92.3)		19 (9.6)	178 (90.4)	
Rural/Small town	93 (59.2)	64 (40.8)		13 (8.3)	144 (91.7)		16 (10.2)	141 (89.8)	
Comprehensive parental postnatal support			0.01			0.04			0.02
Yes	1165 (63.5)	669 (36.5)		170 (9.3)	1663 (90.7)		264 (14.3)	1578 (85.7)	
No	64 (62.7)	38 (37.3)		11 (10.8)	91 (89.2)		16 (15.7)	86 (84.3)	
S1P preoperative variables									
Age at S1P admission (days)	0.80 (3.02)	1.82 (7.52)	-0.18	0.81 (2.80)	1.21 (5.35)	0.09	1.11 (4.21)	1.18 (5.29)	-0.01

Preop enteral feeding			0.02			0.14			0.01
Yes	738 (63.1)	431 (36.9)		98 (8.4)	1070 (91.6)		170 (14.5)	1004 (85.5)	
No	491 (64.0)	276 (36.0)		83 (10.8)	684 (89.2)		110 (14.3)	660 (85.7)	
Any preop breastfeeding			0.33			0.13			0.51
Yes	276 (79.1)	73 (20.9)		41 (11.8)	307 (88.2)		102 (29.1)	248 (70.9)	
No	953 (60.1)	634 (39.9)		140 (8.8)	1447 (91.2)		178 (11.2)	1416 (88.8)	
Preop feeding: Bottle with human milk			0.16			0.02			0.08
Yes	419 (68.9)	189 (31.1)		55 (9.1)	552 (90.9)		79 (13.0)	531 (87.0)	
No	810 (61.0)	518 (39.0)		126 (9.5)	1202 (90.5)		201 (15.1)	1133 (84.9)	
Preop feeding: Bottle with formula			0.36			0.21			0.26
Yes	95 (40.1)	142 (59.9)		12 (5.1)	225 (94.9)		16 (6.7)	223 (93.3)	
No	1134 (66.7)	565 (33.3)		169 (10.0)	1529 (90.0)		264 (15.5)	1441 (84.5)	
Preop feeding: NG trophic			0.05			0.07			0.07
Yes	147 (60.2)	97 (39.8)		19 (7.8)	225 (92.2)		30 (12.2)	215 (87.8)	
No	1082 (63.9)	610 (36.1)		162 (9.6)	1529 (90.4)		250 (14.7)	1449 (85.3)	
Preop feeding: NG > trophic			0.08			0.06			0.10
Yes	53 (55.2)	43 (44.8)		7 (7.3)	89 (92.7)		9 (9.4)	87 (90.6)	
No	1176 (63.9)	664 (36.1)		174 (9.5)	1665 (90.5)		271 (14.7)	1577 (85.3)	
Preop NG nutrition type			0.19			0.19			0.12
Human milk	148 (65.8)	77 (34.2)		22 (9.8)	203 (90.2)		31 (13.8)	194 (86.2)	
Formula	10 (31.2)	22 (68.8)		1 (3.1)	31 (96.9)		3 (9.1)	30 (90.9)	
Human milk + formula	21 (51.2)	20 (48.8)		1 (2.4)	40 (97.6)		3 (7.3)	38 (92.7)	
No preop feeding: Clinical reasons			0.02			0.07			0.02
Yes	364 (64.2)	203 (35.8)		58 (10.2)	509 (89.8)		80 (14.1)	489 (85.9)	
No	865 (63.2)	504 (36.8)		123 (9.0)	1245 (91.0)		200 (14.5)	1175 (85.5)	
No preop feeding: Institutional reasons			0.01			0.15			0.01
Yes	137 (64.3)	76 (35.7)		28 (13.1)	185 (86.9)		30 (14.0)	184 (86.0)	
No	1092 (63.4)	631 (36.6)		153 (8.9)	1569 (91.1)		250 (14.5)	1480 (85.5)	
Preop instability			0.15			0.04			0.25
Yes	482 (59.4)	330 (40.6)		73 (9.0)	739 (91.0)		89 (10.9)	726 (89.1)	
No	747 (66.5)	377 (33.5)		108 (9.6)	1015 (90.4)		191 (16.9)	938 (83.1)	
Preop NEC			0.06			0.11			0.10
Yes	17 (53.1)	15 (46.9)		1 (3.1)	31 (96.9)		2 (6.2)	30 (93.8)	
No	1212 (63.7)	692 (36.3)		180 (9.5)	1723 (90.5)		278 (14.5)	1634 (85.5)	

S1P operative variables									
Age at S1P (days)	7 (10)	12 (19)	-0.30	6 (6)	9 (15)	0.28	6 (6)	10 (15)	-0.31
WAZ at S1P	-0.24 (0.98)	-0.44 (1.13)	0.19	-0.16 (1.05)	-0.33 (1.04)	-0.17	-0.14 (0.90)	-0.34 (1.06)	0.21
Spontaneously breathing at S1P			0.08			0.18			0.06
Yes	975 (64.6)	535 (35.4)		152 (10.1)	1357 (89.9)		225 (14.8)	1291 (85.2)	
No	237 (60.0)	158 (40.0)		26 (6.6)	369 (93.4)		52 (13.1)	345 (86.9)	
Surgery/intervention type			0.11			0.17			0.14
Hybrid Norwood	85 (55.9)	67 (44.1)		13 (8.6)	139 (91.4)		23 (14.9)	131 (85.1)	
Norwood with BTT shunt	286 (62.0)	175 (38.0)		52 (11.3)	409 (88.7)		59 (12.7)	405 (87.3)	
Norwood with RV-PA	741 (65.2)	395 (34.8)		94 (8.3)	1042 (91.7)		161 (14.1)	977 (85.9)	
Other	117 (62.6)	70 (37.4)		22 (11.8)	164 (88.2)		37 (19.7)	151 (80.3)	
Any CPB, CA, or cross clamp			0.07			0.00			0.07
Yes	1131 (64.0)	636 (36.0)		165 (9.3)	1601 (90.7)		250 (14.1)	1522 (85.9)	
No	98 (58.0)	71 (42.0)		16 (9.5)	153 (90.5)		30 (17.4)	142 (82.6)	
Utilized cross clamp			0.02			0.10			0.03
Yes	1060 (63.6)	606 (36.4)		161 (9.7)	1504 (90.3)		238 (14.2)	1433 (85.8)	
No	169 (62.6)	101 (37.4)		20 (7.4)	250 (92.6)		42 (15.4)	231 (84.6)	
CPB duration (minutes)	151 (59)	158 (64)	-0.12	148 (64)	154 (61)	0.10	145 (63)	155 (60)	-0.17
Cross clamp duration (minutes)	66 (35)	67 (35)	-0.03	67 (30)	66 (36)	-0.03	68 (32)	66 (35)	0.04
ECMO in the operating room			0.08			0.11			0.08
Yes	24 (51.1)	23 (48.9)		2 (4.3)	45 (95.7)		4 (8.5)	43 (91.5)	
No	1205 (63.8)	684 (36.2)		179 (9.5)	1709 (90.5)		276 (14.5)	1621 (85.5)	
S1P postoperative variables									
Delayed chest closure			0.06			0.21			0.05
Yes	847 (62.5)	509 (37.5)		110 (8.1)	1245 (91.9)		191 (14.0)	1171 (86.0)	
No	371 (65.5)	195 (34.5)		69 (12.2)	497 (87.8)		87 (15.3)	481 (84.7)	
S1P intubation duration (days)	6.3 (6.2)	8.5 (11.4)	-0.23	6.5 (9.2)	7.2 (8.4)	0.08	5.7 (5.1)	7.3 (8.9)	-0.23
Reintubated within 48 hours			0.14			0.01			0.08
Yes	131 (54.8)	108 (45.2)		22 (9.2)	217 (90.8)		29 (12.0)	212 (88.0)	
No	1097 (64.8)	596 (35.2)		159 (9.4)	1533 (90.6)		251 (14.8)	1448 (85.2)	

Need for S1P cardiac reoperations			0.04			0.03			0.01
Yes	180 (61.0)	115 (39.0)		26 (8.8)	269 (91.2)		42 (14.1)	255 (85.9)	
No	1049 (63.9)	592 (36.1)		155 (9.5)	1485 (90.5)		238 (14.5)	1409 (85.5)	
Postop ECMO			0.13			0.08			0.24
Yes	75 (52.4)	68 (47.6)		10 (7.0)	133 (93.0)		8 (5.6)	136 (94.4)	
No	1151 (64.4)	636 (35.6)		170 (9.5)	1616 (90.5)		272 (15.2)	1522 (84.8)	
Postop instability			0.28			0.12			0.19
Yes	793 (59.3)	544 (40.7)		116 (8.7)	1221 (91.3)		172 (12.8)	1169 (87.2)	
No	436 (72.8)	163 (27.2)		65 (10.9)	533 (89.1)		108 (17.9)	495 (82.1)	
Postop NEC			0.36			0.05			0.09
Yes	81 (38.8)	128 (61.2)		17 (8.1)	192 (91.9)		24 (11.5)	185 (88.5)	
No	1148 (66.5)	579 (33.5)		164 (9.5)	1562 (90.5)		256 (14.8)	1479 (85.2)	
Postop bronchoscopy			0.11			0.13			0.12
Yes	44 (51.8)	41 (48.2)		13 (15.3)	72 (84.7)		7 (8.2)	78 (91.8)	
No	1185 (64.0)	666 (36.0)		168 (9.1)	1682 (90.9)		273 (14.7)	1586 (85.3)	
Postop laryngoscopy to assess vocal cords			0.18			0.14			0.25
Yes	305 (56.8)	232 (43.2)		40 (7.4)	497 (92.6)		52 (9.6)	487 (90.4)	
No	924 (66.0)	475 (34.0)		141 (10.1)	1257 (89.9)		228 (16.2)	1177 (83.8)	
Postop diaphragm plication			0.13			0.03			0.05
Yes	25 (45.5)	30 (54.5)		6 (10.9)	49 (89.1)		6 (10.9)	49 (89.1)	
No	1204 (64.0)	677 (36.0)		175 (9.3)	1705 (90.7)		274 (14.5)	1615 (85.5)	
Postop fundoplication			0.16			0.07			0.28
Yes	26 (41.9)	36 (58.1)		4 (6.5)	58 (93.5)		0 (0.0)	62 (100.0)	
No	1203 (64.2)	671 (35.8)		177 (9.5)	1696 (90.5)		280 (14.9)	1602 (85.1)	
Postop G-tube procedure			0.37			0.29			0.53
Yes	200 (46.9)	226 (53.1)		22 (5.2)	404 (94.8)		17 (4.0)	411 (96.0)	
No	1029 (68.1)	481 (31.9)		159 (10.5)	1350 (89.5)		263 (17.3)	1253 (82.7)	
Postop time to enteral feeds (days)	4.7 (3.7)	6.5 (16.5)	-0.18	4.9 (4.1)	5.4 (10.9)	0.05	4.7 (4.2)	5.5 (11.1)	-0.09
Postop time to full feeds (days)	13 (11)	15 (13)	-0.16	15 (15)	14 (12)	-0.07	12 (10)	14 (12)	-0.16
Weaned inotropes/vasoactive meds within 5 days			0.10			0.15			0.19
Yes	393 (67.0)	194 (33.0)		66 (11.3)	520 (88.7)		106 (18.0)	484 (82.0)	
No	836 (62.0)	513 (38.0)		115 (8.5)	1234 (91.5)		174 (12.9)	1180 (87.1)	

S1P discharge variables									
WAZ at discharge	-1.68 (1.02)	-1.92 (1.02)	0.24	-1.67 (1.07)	-1.77 (1.02)	-0.10	-1.46 (0.92)	-1.82 (1.04)	0.36
LAZ at discharge	-1.59 (1.81)	-1.92 (1.92)	0.17	-1.58 (1.87)	-1.72 (1.86)	-0.08	-1.22 (1.51)	-1.79 (1.90)	0.33
Any breastfeeding at discharge						0.49			
Yes	N/A	N/A		59 (21.1)	220 (78.9)		N/A	N/A	
No	N/A	N/A		122 (7.4)	1534 (92.6)		N/A	N/A	
Bottle feeding at discharge			0.19			0.08			0.20
Yes	844 (66.6)	423 (33.4)		112 (8.8)	1154 (91.2)		205 (16.1)	1065 (83.9)	
No	385 (57.5)	284 (42.5)		69 (10.3)	600 (89.7)		75 (11.1)	599 (88.9)	
NG/NJ tube at discharge			0.16			0.09			0.31
Yes	549 (67.9)	259 (32.1)		68 (8.4)	740 (91.6)		82 (10.1)	730 (89.9)	
No	680 (60.3)	448 (39.7)		113 (10.0)	1014 (90.0)		198 (17.5)	934 (82.5)	
G-tube at discharge			0.41			0.33			0.56
Yes	221 (46.6)	253 (53.4)		23 (4.9)	451 (95.1)		20 (4.2)	456 (95.8)	
No	1008 (68.9)	454 (31.1)		158 (10.8)	1303 (89.2)		260 (17.7)	1208 (82.3)	
Fortified feeding at discharge[b]			0.09			1.00			0.32
Yes	1111 (62.8)	658 (37.2)		99 (5.6)	1669 (94.4)		233 (13.1)	1541 (86.9)	
No	97 (70.8)	40 (29.2)		73 (53.3)	64 (46.7)		43 (31.2)	95 (68.8)	
Aortic obstruction at discharge			0.07			0.02			0.04
Yes	41 (71.9)	16 (28.1)		6 (10.5)	51 (89.5)		10 (17.5)	47 (82.5)	
No	999 (63.2)	581 (36.8)		153 (9.7)	1426 (90.3)		232 (14.6)	1355 (85.4)	
Tricuspid/systemic AV regurgitation at discharge			0.01			0.14			0.09
Moderate/severe	202 (63.3)	117 (36.7)		22 (6.9)	297 (93.1)		55 (17.1)	267 (82.9)	
Normal/mild	1010 (63.8)	574 (36.2)		159 (10.0)	1424 (90.0)		223 (14.0)	1366 (86.0)	
Oxygen saturation at discharge	82.9 (5.7)	82.2 (4.9)	0.12	82.8 (5.2)	82.6 (5.5)	-0.04	82.9 (5.3)	82.6 (5.4)	0.05
# of cardiac meds at discharge	2.19 (0.86)	2.30 (0.96)	-0.12	2.15 (0.98)	2.24 (0.90)	0.09	2.09 (0.89)	2.26 (0.90)	-0.19
Parental 24-hour room in care before S1P discharge			0.00			0.36			0.04
Yes	1134 (63.4)	654 (36.6)		150 (8.4)	1637 (91.6)		259 (14.4)	1536 (85.6)	
No	53 (63.9)	30 (36.1)		23 (27.7)	60 (72.3)		10 (11.9)	74 (88.1)	
S1P length of stay (days)	40 (25)	61 (38)	-0.64	39 (32)	49 (32)	0.29	34 (17)	50 (34)	-0.58

	At stage 2 palliation n (%) or mean (SD)								
	Any human milk feeding			Exclusive human milk feeding			Direct breastfeeding		
	Any n = 467	None n = 810	SMD	Exclusive n = 115	Not exclusive n = 1146	SMD	Any n = 157	None n = 1421	SMD
Prenatal variables									
Fetal diagnosis			0.16			0.08			0.03
Yes	419 (37.9)	686 (62.1)		101 (9.3)	989 (90.7)		135 (9.9)	1225	
No	45 (27.3)	120 (72.7)		12 (7.4)	150 (92.6)		19 (9.1)	190 (90.9)	
Characteristics at birth									
Birth year			0.22			0.38			0.09
2016	18 (64.3)	10 (35.7)		8 (36.4)	14 (63.6)		13 (9.0)	132 (91.0)	
2017	50 (41.0)	72 (59.0)		16 (14.2)	97 (85.8)		26 (8.7)	274 (91.3)	
2018	110 (32.0)	234 (68.0)		26 (7.6)	318 (92.4)		35 (10.1)	313 (89.9)	
2019	128 (34.1)	247 (65.9)		27 (7.2)	346 (92.8)		40 (10.7)	335 (89.3)	
2020	133 (39.3)	205 (60.7)		33 (9.8)	304 (90.2)		36 (10.7)	302 (89.3)	
2021	28 (40.0)	42 (60.0)		5 (7.1)	65 (92.9)		7 (10.0)	63 (90.0)	
Born at the NPC-QIC center			0.15			0.24			0.26
Yes	286 (39.5)	438 (60.5)		77 (10.8)	633 (89.2)		107 (11.9)	790 (88.1)	
No	181 (32.7)	372 (67.3)		38 (6.9)	511 (93.1)		50 (7.4)	629 (92.6)	
Preterm (<37 weeks)			0.12			0.35			0.21
Yes	32 (28.1)	82 (71.9)		2 (1.8)	111 (98.2)		6 (4.4)	129 (95.6)	
No	431 (37.3)	723 (62.7)		111 (9.8)	1027 (90.2)		147 (10.3)	1280	
WAZ at birth	-0.04 (0.92)	-0.18 (1.05)	0.15	0.15 (0.91)	-0.16 (1.01)	0.32	0.04 (0.84)	-0.12	0.16
Primary cardiac diagnosis			0.09			0.12			0.24
HLHS	34 (30.1)	79 (69.9)		7 (6.2)	105 (93.8)		5 (3.8)	127 (96.2)	
Other SV	433 (37.2)	731 (62.8)		108 (9.4)	1039 (90.6)		152 (10.5)	1292	
Major genetic syndrome			0.13			0.20			0.14
Yes	16 (24.2)	50 (75.8)		2 (3.1)	63 (96.9)		4 (5.0)	76 (95.0)	
No	451 (37.2)	760 (62.8)		113 (9.5)	1081 (90.5)		153 (10.2)	1343	

Other major anomaly			0.05			0.11			0.01
Yes	331 (35.8)	594 (64.2)		78 (8.6)	834 (91.4)		116 (10.0)	1040	
No	136 (38.6)	216 (61.4)		37 (10.7)	310 (89.3)		41 (9.8)	379 (90.2)	
Sex			0.00			0.03			0.00
Female	171 (36.5)	298 (63.5)		41 (8.9)	422 (91.1)		59 (10.0)	531 (90.0)	
Male	296 (36.6)	512 (63.4)		74 (9.3)	722 (90.7)		98 (9.9)	888 (90.1)	
Race			0.39			0.49			0.28
Another race/Multi-race	50 (34.0)	97 (66.0)		9 (6.2)	137 (93.8)		12 (6.7)	166 (93.3)	
Black/African American	32 (16.9)	157 (83.1)		4 (2.1)	183 (97.9)		13 (5.6)	220 (94.4)	
White	367 (40.8)	533 (59.2)		100 (11.3)	785 (88.7)		126 (11.2)	998 (88.8)	
Hispanic or Latino/a ethnicity			0.05			0.22			0.14
Yes	63 (33.3)	126 (66.7)		10 (5.4)	175 (94.6)		16 (6.9)	215 (93.1)	
No	377 (36.7)	650 (63.3)		102 (10.1)	912 (89.9)		130 (10.1)	1151	
Insurance type			0.65			0.64			0.48
Government	137 (22.0)	486 (78.0)		26 (4.2)	593 (95.8)		44 (5.7)	730 (94.3)	
Private/Self	302 (50.3)	298 (49.7)		82 (14.0)	505 (86.0)		101 (13.6)	639 (86.4)	
Median income of residential ZCTA	72,051 (25,272)	63,006 (22,392)	0.38	72,097 (23,554)	65,823 (23,937)	0.26	71,857 (24,006)	65,620 (24,104)	0.26
SDI score of residential ZCTA[a]	45 (28)	53 (28)	-0.31	41 (27)	51 (28)	-0.36	47 (28)	50 (28)	-0.11
Rural-urban commuting area			0.05			0.13			0.13
Metropolitan	373 (36.8)	640 (63.2)		95 (9.5)	905 (90.5)		129 (10.3)	1122	
Micropolitan	53 (38.7)	84 (61.3)		13 (9.8)	119 (90.2)		18 (11.0)	146 (89.0)	
Rural/Small town	33 (33.0)	67 (67.0)		6 (6.0)	94 (94.0)		8 (6.4)	117 (93.6)	
Comprehensive parental postnatal support			0.08			0.03			0.02
Yes	437 (36.1)	772 (63.9)		108 (9.1)	1083 (90.9)		148 (9.9)	1344 (90.1)	
No	30 (44.1)	38 (55.9)		7 (10.3)	61 (89.7)		9 (10.7)	75 (89.3)	
S1P preoperative variables									
Age at S1P admission (days)	0.77 (2.98)	1.30 (6.03)	-0.11	0.43 (1.24)	1.18 (5.40)	-0.19	0.98 (4.08)	1.16 (5.28)	-0.04
Preop enteral feeding			0.01			0.09			0.04
Yes	282 (36.3)	495 (63.7)		75 (9.7)	695 (90.3)		97 (10.2)	851 (89.8)	
No	185 (37.0)	315 (63.0)		40 (8.2)	449 (91.8)		60 (9.6)	568 (90.4)	

Any preop breastfeeding			0.40			0.32			0.51
Yes	132 (56.7)	101 (43.3)		35 (15.3)	194 (84.7)		60 (20.8)	229 (79.2)	
No	335 (32.1)	709 (67.9)		80 (7.8)	950 (92.2)		97 (7.5)	1190 (92.5)	
Preop feeding: Bottle with human milk			0.07			0.16			0.21
Yes	143 (34.1)	276 (65.9)		46 (11.0)	372 (89.0)		36 (7.3)	459 (92.7)	
No	324 (37.8)	534 (62.2)		69 (8.2)	772 (91.8)		121 (11.2)	960 (88.8)	
Preop feeding: Bottle with formula			0.23			0.16			0.15
Yes	36 (22.9)	121 (77.1)		9 (5.8)	146 (94.2)		13 (6.6)	185 (93.4)	
No	431 (38.5)	689 (61.5)		106 (9.6)	998 (90.4)		144 (10.4)	1234 (89.6)	
Preop feeding: NG trophic			0.13			0.12			0.12
Yes	43 (28.5)	108 (71.5)		10 (6.7)	140 (93.3)		14 (7.2)	181 (92.8)	
No	424 (37.7)	702 (62.3)		105 (9.5)	1004 (90.5)		143 (10.4)	1238 (89.6)	
Preop feeding: NG > trophic			0.12			0.15			0.10
Yes	12 (23.1)	40 (76.9)		2 (3.8)	50 (96.2)		4 (6.2)	61 (93.8)	
No	455 (37.1)	770 (62.9)		113 (9.4)	1094 (90.6)		153 (10.1)	1358 (89.9)	
Preop NG nutrition type			0.20[b]			0.30			0.14
Human milk	46 (33.3)	92 (66.7)		12 (8.8)	125 (91.2)		14 (8.3)	155 (91.7)	
Formula	3 (12.5)	21 (87.5)		0 (0.0)	24 (100.0)		1 (3.8)	25 (96.2)	
Human milk + formula	5 (20.8)	19 (79.2)		0 (0.0)	24 (100.0)		2 (6.7)	28 (93.3)	
No preop feeding: Clinical reasons			0.05			0.16			0.00
Yes	146 (38.2)	236 (61.8)		27 (7.2)	347 (92.8)		46 (9.9)	418 (90.1)	
No	321 (35.9)	574 (64.1)		88 (9.9)	797 (90.1)		111 (10.0)	1001 (90.0)	
No preop feeding: Institutional reasons			0.05			0.05			0.08
Yes	42 (33.1)	85 (66.9)		13 (10.5)	111 (89.5)		14 (7.9)	163 (92.1)	
No	425 (37.0)	725 (63.0)		102 (9.0)	1033 (91.0)		143 (10.2)	1256 (89.8)	
Preop instability			0.19			0.17			0.33
Yes	160 (31.2)	353 (68.8)		38 (7.5)	469 (92.5)		43 (6.6)	609 (93.4)	
No	307 (40.2)	457 (59.8)		77 (10.2)	675 (89.8)		114 (12.3)	810 (87.7)	
Preop NEC			0.01			0.19			0.10
Yes	8 (38.1)	13 (61.9)		0 (0.0)	21 (100.0)		1 (4.0)	24 (96.0)	
No	459 (36.5)	797 (63.5)		115 (9.3)	1123 (90.7)		156 (10.1)	1395 (89.9)	
S1P operative variables									
Age at S1P (days)	7 (10)	10 (15)	-0.19	6 (6)	9 (14)	-0.26	6 (5)	9 (13)	-0.26
WAZ at S1P	-0.13 (0.94)	-0.36 (1.04)	0.23	0.03 (0.89)	-0.31 (1.02)	0.36	-0.08 (0.90)	-0.29 (1.02)	0.22

Spontaneously breathing at S1P			0.02			0.29			0.10
Yes	366 (36.7)	630 (63.3)		100 (10.2)	883 (89.8)		118 (9.5)	1118 (90.5)	
No	91 (35.4)	166 (64.6)		12 (4.8)	240 (95.2)		37 (11.9)	274 (88.1)	
Surgery/intervention type			0.12			0.16			0.14
Hybrid Norwood	17 (25.8)	49 (74.2)		4 (6.1)	62 (93.9)		5 (5.6)	84 (94.4)	
Norwood with BTT shunt	116 (38.8)	183 (61.2)		30 (10.2)	265 (89.8)		39 (10.1)	347 (89.9)	
Norwood with RV-PA	288 (36.7)	497 (63.3)		66 (8.5)	709 (91.5)		96 (10.0)	862 (90.0)	
Other	46 (36.2)	81 (63.8)		15 (12.2)	108 (87.8)		17 (11.9)	126 (88.1)	
Any CPB, CA, or cross clamp			0.09			0.06			0.05
Yes	443 (37.1)	751 (62.9)		109 (9.3)	1067 (90.7)		148 (10.1)	1319 (89.9)	
No	24 (28.9)	59 (71.1)		6 (7.2)	77 (92.8)		9 (8.3)	100 (91.7)	
Utilized cross clamp			0.03			0.16			0.03
Yes	418 (36.8)	717 (63.2)		107 (9.6)	1010 (90.4)		139 (10.1)	1243 (89.9)	
No	49 (34.5)	93 (65.5)		8 (5.6)	134 (94.4)		18 (9.3)	176 (90.7)	
CPB duration (minutes)	147 (56)	154 (57)	-0.11	142 (52)	153 (57)	-0.20	146 (57)	154 (57)	-0.14
Cross clamp duration (minutes)	68 (35)	67 (35)	0.01	68 (31)	67 (36)	0.02	68 (33)	66 (35)	0.07
ECMO in the operating			0.10			0.15			0.01
Yes	14 (53.8)	12 (46.2)		5 (19.2)	21 (80.8)		3 (9.1)	30 (90.9)	
No	453 (36.2)	798 (63.8)		110 (8.9)	1123 (91.1)		154 (10.0)	1389 (90.0)	
S1P postoperative variables									
Delayed chest closure			0.10			0.12			0.19
Yes	342 (37.9)	560 (62.1)		75 (8.4)	813 (91.6)		121 (10.9)	989 (89.1)	
No	120 (32.8)	246 (67.2)		39 (10.8)	323 (89.2)		33 (7.3)	420 (92.7)	
S1P intubation duration (days)	6.5 (5.4)	7.1 (9.9)	-0.07	6.2 (4.8)	7.0 (8.9)	-0.10	5.8 (3.8)	6.8 (8.4)	-0.16
Reintubated within 48 hours			0.10			0.07			0.23
Yes	48 (30.6)	109 (69.4)		12 (7.7)	143 (92.3)		10 (5.1)	187 (94.9)	
No	419 (37.5)	698 (62.5)		103 (9.4)	998 (90.6)		147 (10.7)	1229 (89.3)	
Need for S1P cardiac reoperations			0.08			0.04			0.01
Yes	79 (40.7)	115 (59.3)		19 (9.9)	173 (90.1)		22 (9.8)	202 (90.2)	
No	388 (35.8)	695 (64.2)		96 (9.0)	971 (91.0)		135 (10.0)	1217 (90.0)	

Postop ECMO			0.02			0.08			0.11
Yes	31 (35.2)	57 (64.8)		6 (6.8)	82 (93.2)		7 (6.6)	99 (93.4)	
No	435 (36.7)	751 (63.3)		108 (9.2)	1060 (90.8)		150 (10.2)	1317 (89.8)	
Postop instability			0.15			0.13			0.27
Yes	299 (34.2)	576 (65.8)		73 (8.4)	794 (91.6)		88 (8.2)	979 (91.8)	
No	168 (41.8)	234 (58.2)		42 (10.7)	350 (89.3)		69 (13.6)	440 (86.4)	
Postop NEC			0.13			0.04			0.10
Yes	37 (27.8)	96 (72.2)		11 (8.3)	122 (91.7)		12 (7.4)	150 (92.6)	
No	430 (37.6)	714 (62.4)		104 (9.2)	1022 (90.8)		145 (10.3)	1269 (89.7)	
Postop bronchoscopy			0.05			0.09			0.04
Yes	16 (31.4)	35 (68.6)		3 (5.9)	48 (94.1)		5 (8.1)	57 (91.9)	
No	451 (36.8)	775 (63.2)		112 (9.3)	1096 (90.7)		152 (10.0)	1362 (90.0)	
Postop laryngoscopy to assess vocal cords			0.18			0.13			0.20
Yes	106 (29.9)	248 (70.1)		26 (7.4)	324 (92.6)		32 (7.3)	408 (92.7)	
No	361 (39.1)	562 (60.9)		89 (9.8)	820 (90.2)		125 (11.0)	1011 (89.0)	
Postop diaphragm plication			0.07			0.24			0.25
Yes	9 (27.3)	24 (72.7)		0 (0.0)	33 (100.0)		0 (0.0)	43 (100.0)	
No	458 (36.8)	786 (63.2)		115 (9.4)	1111 (90.6)		157 (10.2)	1376 (89.8)	
Postop fundoplication			0.12			0.24			0.20
Yes	6 (19.4)	25 (80.6)		0 (0.0)	31 (100.0)		1 (2.0)	48 (98.0)	
No	461 (37.0)	785 (63.0)		115 (9.4)	1113 (90.6)		156 (10.2)	1371 (89.8)	
Postop G-tube procedure			0.18			0.28			0.48
Yes	70 (28.3)	177 (71.7)		12 (4.9)	234 (95.1)		9 (2.8)	311 (97.2)	
No	397 (38.5)	633 (61.5)		103 (10.2)	910 (89.8)		148 (11.8)	1108 (88.2)	
Postop time to enteral feeds (days)	5.2 (4.4)	5.1 (8.2)	0.02	4.4 (3.5)	5.2 (7.4)	-0.13	4.7 (3.6)	5.2 (6.9)	-0.08
Postop time to full feeds (days)	14 (10)	14 (12)	0.01	12 (8)	14 (12)	-0.17	13 (10)	14 (12)	-0.06
Weaned inotropes/vasoactive meds within 5 days			0.06			0.04			0.25
Yes	147 (38.8)	232 (61.2)		36 (9.7)	335 (90.3)		65 (13.4)	421 (86.6)	
No	320 (35.6)	578 (64.4)		79 (8.9)	809 (91.1)		92 (8.4)	998 (91.6)	
S1P discharge variables									
WAZ at discharge	-1.58 (0.97)	-1.81 (1.03)	0.24	-1.34 (0.96)	-1.77 (1.01)	0.44	-1.44 (0.88)	-1.75 (1.01)	0.32
LAZ at discharge	-1.25 (1.64)	-1.92 (1.92)	0.38	-1.01 (1.91)	-1.75 (1.84)	0.40	-1.03 (1.54)	-1.70 (1.86)	0.40

Any breastfeeding at discharge			0.69			0.50			1.40
Yes	154 (73.3)	56 (26.7)		40 (20.2)	158 (79.8)		102 (42.5)	138 (57.5)	
No	313 (29.3)	754 (70.7)		75 (7.1)	986 (92.9)		55 (4.1)	1281 (95.9)	
Bottle feeding at discharge			0.03			0.05			0.15
Yes	326 (37.1)	553 (62.9)		81 (9.4)	782 (90.6)		116 (10.9)	952 (89.1)	
No	141 (35.4)	257 (64.6)		34 (8.6)	362 (91.4)		41 (8.1)	467 (91.9)	
NG/NJ tube at discharge			0.04			0.07			0.28
Yes	201 (37.6)	333 (62.4)		52 (9.8)	478 (90.2)		47 (7.1)	616 (92.9)	
No	266 (35.8)	477 (64.2)		63 (8.6)	666 (91.4)		110 (12.0)	803 (88.0)	
G-tube at discharge			0.22			0.29			0.51
Yes	76 (27.2)	203 (72.8)		14 (5.0)	265 (95.0)		10 (2.8)	343 (97.2)	
No	391 (39.2)	607 (60.8)		101 (10.3)	879 (89.7)		147 (12.0)	1076 (88.0)	
Fortified feeding at discharge[b]			0.05			0.45			0.24
Yes	419 (36.2)	737 (63.8)		86 (7.6)	1052 (92.4)		134 (9.3)	1300 (90.7)	
No	39 (40.6)	57 (59.4)		24 (25.0)	72 (75.0)		22 (19.0)	94 (81.0)	
Aortic obstruction at discharge			0.06			0.06			0.08
Yes	9 (29.0)	22 (71.0)		2 (6.5)	29 (93.5)		3 (6.5)	43 (93.5)	
No	384 (36.6)	664 (63.4)		96 (9.3)	937 (90.7)		128 (9.9)	1163 (90.1)	
Tricuspid/systemic AV regurgitation at discharge			0.04			0.04			0.08
Moderate/severe	66 (34.4)	126 (65.6)		16 (8.4)	174 (91.6)		20 (8.4)	218 (91.6)	
Normal/mild	397 (37.2)	671 (62.8)		99 (9.4)	953 (90.6)		137 (10.4)	1178 (89.6)	
Oxygen saturation at discharge	82.8 (5.1)	82.5 (5.6)	0.06	83.2 (4.8)	82.5 (5.5)	0.14	83.2 (5.8)	82.5 (5.3)	0.12
# of cardiac meds at discharge	2.23 (0.85)	2.22 (0.89)	0.01	2.21 (0.80)	2.23 (0.88)	-0.03	2.15 (0.83)	2.23 (0.89)	-0.10
Parental 24-hour room in care before S1P discharge			0.12			0.11			0.08
Yes	431 (35.9)	770 (64.1)		108 (9.1)	1076 (90.9)		144 (9.9)	1316 (90.1)	
No	21 (52.5)	19 (47.5)		6 (15.0)	34 (85.0)		9 (13.6)	57 (86.4)	
S1P length of stay (days)	41 (24)	49 (32)	-0.27	36 (20)	47 (30)	-0.41	34 (15)	47 (29)	-0.53
Interstage variables									
Number of interstage readmissions	0.77 (1.00)	1.01 (1.29)	-0.21	0.75 (0.95)	0.94 (1.22)	-0.17	0.71 (0.94)	0.99 (1.26)	-0.25
Admission diagnosis: Bloody stool			0.03			0.16			0.04

Yes	22 (33.3)	44 (66.7)		10 (15.4)	55 (84.6)		10 (11.4)	78 (88.6)	
No	445 (36.7)	766 (63.3)		105 (8.8)	1089 (91.2)		147 (9.9)	1341 (90.1)	
Admission diagnosis: Cyanosis			0.05			0.10			0.00
Yes	90 (39.0)	141 (61.0)		25 (11.0)	202 (89.0)		28 (9.9)	254 (90.1)	
No	377 (36.0)	669 (64.0)		90 (8.7)	942 (91.3)		129 (10.0)	1165 (90.0)	
Admission diagnosis: GERD			0.08			0.22			0.24
Yes	7 (25.0)	21 (75.0)		0 (0.0)	28 (100.0)		0 (0.0)	40 (100.0)	
No	460 (36.8)	789 (63.2)		115 (9.3)	1116 (90.7)		157 (10.2)	1379 (89.8)	
Admission diagnosis: Pneumonia			0.19			0.14			0.11
Yes	8 (16.3)	41 (83.7)		2 (4.1)	47 (95.9)		3 (5.3)	54 (94.7)	
No	459 (37.4)	769 (62.6)		113 (9.3)	1097 (90.7)		154 (10.1)	1365 (89.9)	
Admission diagnosis: Procedure for residual lesion			0.05			0.11			0.02
Yes	12 (44.4)	15 (55.6)		1 (3.7)	26 (96.3)		4 (11.4)	31 (88.6)	
No	455 (36.4)	795 (63.6)		114 (9.3)	1118 (90.7)		153 (9.9)	1388 (90.1)	
Admission diagnosis: Respiratory distress			0.20			0.20			0.18
Yes	11 (17.2)	53 (82.8)		2 (3.1)	62 (96.9)		3 (3.9)	73 (96.1)	
No	456 (37.6)	757 (62.4)		113 (9.5)	1082 (90.5)		154 (10.3)	1346 (89.7)	
Admission diagnosis: Vomiting/diarrhea			0.14			0.24			0.29
Yes	29 (26.4)	81 (73.6)		4 (3.6)	106 (96.4)		4 (2.9)	134 (97.1)	
No	438 (37.5)	729 (62.5)		111 (9.7)	1038 (90.3)		153 (10.6)	1285 (89.4)	
Admission diagnosis: Weight gain			0.11			0.12			0.10
Yes	20 (26.3)	56 (73.7)		4 (5.4)	70 (94.6)		7 (6.9)	95 (93.1)	
No	447 (37.2)	754 (62.8)		111 (9.4)	1074 (90.6)		150 (10.2)	1324 (89.8)	
Admission diagnosis: Wound infection/dehiscence			0.02			0.07			0.07
Yes	13 (39.4)	20 (60.6)		2 (6.1)	31 (93.9)		6 (14.3)	36 (85.7)	
No	454 (36.5)	790 (63.5)		113 (9.2)	1113 (90.8)		151 (9.8)	1383 (90.2)	
Major interstage procedure			0.16			0.06			0.17
Yes	196 (32.6)	405 (67.4)		51 (8.6)	540 (91.4)		64 (8.4)	695 (91.6)	
No	271 (40.1)	405 (59.9)		64 (9.6)	604 (90.4)		93 (11.4)	724 (88.6)	
Number of interstage procedures	0.66 (0.92)	0.89 (1.18)	-0.23	0.69 (0.89)	0.82 (1.12)	-0.13	0.61 (0.89)	0.86 (1.15)	-0.24
Major adverse event			0.08			0.12			0.22
Yes	12 (26.7)	33 (73.3)		2 (4.5)	42 (95.5)		1 (1.8)	54 (98.2)	
No	455 (36.9)	777 (63.1)		113 (9.3)	1102 (90.7)		156 (10.3)	1365 (89.7)	
S2P variables									

Age at S2P (days)	143 (42)	158 (50)	-0.31	144 (38)	154 (49)	-0.21	145 (37)	153 (49)	-0.19
WAZ at S2P	-1.30 (1.05)	-1.32 (1.07)	0.02	-1.06 (1.15)	-1.35 (1.04)	0.26	-1.18 (0.95)	-1.32 (1.06)	0.14
LAZ at S2P	-1.15 (1.51)	-1.35 (1.59)	0.13	-0.94 (1.46)	-1.31 (1.58)	0.25	-0.89 (1.56)	-1.33 (1.52)	0.28
Any breastfeeding at S2P			–			0.94			–
Yes	–	–		52 (37.4)	87 (62.6)		–	–	
No	–	–		63 (5.6)	1057 (94.4)		–	–	
Bottle feeding at S2P			0.07			0.33			0.06
Yes	312 (37.7)	516 (62.3)		58 (7.1)	758 (92.9)		106 (10.4)	917 (89.6)	
No	155 (34.5)	294 (65.5)		57 (12.9)	386 (87.1)		51 (9.2)	502 (90.8)	
NG/NJ tube at S2P			0.02			0.27			0.55
Yes	135 (35.9)	241 (64.1)		22 (5.9)	352 (94.1)		15 (3.3)	439 (96.7)	
No	332 (36.8)	569 (63.2)		93 (10.5)	792 (89.5)		142 (12.7)	980 (87.3)	
G-tube at S2P			0.18			0.29			0.49
Yes	85 (29.0)	208 (71.0)		15 (5.1)	277 (94.9)		12 (3.2)	362 (96.8)	
No	382 (38.8)	602 (61.2)		100 (10.3)	867 (89.7)		145 (12.1)	1057 (87.9)	
Aortic obstruction at S2P			0.03			0.08			0.07
Yes	17 (33.3)	34 (66.7)		6 (11.8)	45 (88.2)		8 (11.6)	61 (88.4)	
No	271 (35.8)	486 (64.2)		66 (8.9)	678 (91.1)		86 (9.2)	849 (90.8)	
Oxygen saturation at S2P	79.3 (5.4)	79.5 (5.7)	-0.04	78.8 (5.1)	79.5 (5.7)	-0.14	79.4 (5.5)	79.5 (5.5)	-0.01

Abbreviations: AV = atrioventricular valve; BTT = Blalock-Thomas-Taussig; CA = circulatory arrest; CPB = cardiopulmonary bypass; ECMO = extracorporeal membrane oxygenation; GERD = gastroesophageal reflux disease; G-tube = gastrostomy tube; HLHS = hypoplastic left heart syndrome; LAZ = length-for-age z-score; meds = medication; NEC = necrotizing enterocolitis; NG = nasogastric; NJ = nasojejunal; NPC-QIC = National Pediatric Cardiology Quality Improvement Collaborative; PA = pulmonary artery; postop = postoperative; preop = preoperative; RV = right ventricle; S1P = stage 1 palliation; S2P = stage 2 palliation; SDI = social deprivation index; SMD = standardized mean difference; SV = single ventricle; TR = tricuspid/systemic valve regurgitation; WAZ = weight-for-age z-score; ZCTA = zip code tabulation area.
Note: Percentages refer to the proportion of nonmissing data.
[a]SDI score range, 0–100. Higher numbers indicate a higher level of social deprivation.
[b]Fortified feeding = a calorie goal of ≥ 22 kcal/oz.

importance scores (ie, absolute value of the t-statistic; range 0–100) were calculated for test sets. Variables with estimates ≠0 in ≥50% of imputations were retained.[35] We entered the retained variables into a final elastic net logistic regression model for each imputed dataset, using the *MAMI* package[36] to combine results and obtain bootstrap 95% confidence intervals (CI; n=100 bootstraps). Variables with unexponentiated point estimates ≠0 are presented with odds ratios (OR), CIs, and averaged variable importance scores. As a sensitivity analysis, we conducted unpenalized logistic regression on the imputed data including the same retained variables.

NPC-QIC site analysis. Due to site size variability, we could not include NPC-QIC site in the elastic net models. Therefore, we performed standard logistic regression with complete case data including the previously retained variables. We added NPC-QIC site (de-identified) to the models and conducted likelihood ratio tests to determine model improvement We calculated ORs and 95% CIs for each feeding outcome at each NPC-QIC site, including the top 3 quartiles for size (n>10 infants) and adjusting for race and insurance type.[37]

Results

Of 2693 infants in the NPC-QIC registry, 1944 (72.2%) infants from 67 sites met eligibility criteria for S1P analysis, and 1578 (58.6%) met criteria for S2P analysis. Demographic characteristics and diagnoses of included participants can be found in Table 4.2.

Table 4.2. Sample Characteristics (N = 1944)

	n (%) or mean (SD)
Sex	
Female	763 (39.2)
Male	1181 (60.8)
Race	
Another race/Multi-race	223 (11.8)
Black/African American	299 (15.8)
White	1370 (72.4)
(Missing)	52
Hispanic or Latino/a ethnicity	
Yes	303 (16.3)
No	1559 (83.7)

(Missing)	82
Insurance	
Government	992 (52.9)
Private/Self	883 (47.1)
(Missing)	69
Rural-urban commuting area	
Metropolitan	1541 (81.3)
Micropolitan	197 (10.4)
Rural/Small town	157 (8.3)
(Missing)	49
Median income of residential ZCTA	65,855 (23,909)
(Missing)	53
SDI score of residential ZCTA[a]	51 (28)
(Missing)	50
Born at the NPC-QIC center	
Yes	1102 (56.7)
No	842 (43.3)
Birth WAZ	-0.14 (1.09)
(Missing)	55
Preterm (<37 weeks)	
Yes	197 (10.2)
No	1728 (89.8)
(Missing)	19
Age at S1P admission (days)	1.17 (5.15)
Primary cardiac diagnosis	
HLHS	1357 (69.8)
Other SV	587 (30.2)
Major genetic syndrome	
Yes	216 (11.1)
No	1728 (88.9)
Other major anomaly	
Yes	115 (5.9)
No	1829 (94.1)
Age at S1P discharge (days)	49 (33)

Abbreviations: HLHS = hypoplastic left heart syndrome; NPC-QIC = National Pediatric Cardiology Quality Improvement. Collaborative; S1P = stage 1 palliation; SD = standard deviation; SDI = social deprivation index; SV = single ventricle; WAZ = weight-for-age z-score; ZCTA = zip code tabulation area.
Note: Percentages refer to the proportion of nonmissing data.
[a]SDI score range, 0–100. Higher numbers indicate a higher level of social deprivation.

The initial bivariate analyses of differences between infants who received HM/BF and those who did not, at both time points, can be found in Table 4.1. A total of 254 (13.9%) infants completed S1P but remained inpatient until S2P and were excluded. Differences between infants who remained inpatient and those who were discharged can be seen in Table 4.3. Infants who were not discharged were more likely to be born preterm, more likely to receive government insurance, less likely to be enterally fed

Table 4.3. Differences Between Infants Discharged After S1P and Infants Remaining Inpatient Until S2P (N = 1832)

	Not discharged (n = 254)	Discharged (n = 1578)	SMD[a]
	n (%) or mean (SD)		
Sex			0.03
Female	91 (35.8)	590 (37.4)	
Male	163 (64.2)	986 (62.6)	
Race			0.16
Another race/Multi-race	35 (14.2)	178 (11.6)	
Black/African American	49 (19.9)	233 (15.2)	
White	162 (65.9)	1126 (73.3)	
Hispanic or Latino/a ethnicity			0.06
Yes	43 (17.6)	231 (15.3)	
No	201 (82.4)	1283 (84.7)	
Insurance			0.23
Government	144 (62.3)	776 (51.2)	
Private/Self	87 (37.7)	740 (48.8)	
Rural-urban commuting area			0.10
Metropolitan	199 (79.0)	1253 (81.3)	
Micropolitan	25 (9.9)	164 (10.6)	
Rural/Small town	28 (11.1)	125 (8.1)	
Median income of residential ZCTA	61,961 (23,299)	66,235 (24,149)	0.18
SDI score of residential ZCTA[b]	56 (29)	50 (28)	-0.22
Born at the NPC-QIC center			0.12
Yes	129 (50.8)	898 (56.9)	
No	125 (49.2)	680 (43.1)	
Birth WAZ	-0.12 (1.14)	-0.11 (1.09)	0.01
Preterm (<37 weeks)	42 (16.7)	136 (8.7)	0.24
Primary cardiac diagnosis			0.05
HLHS	180 (70.9)	1157 (73.3)	
Other SV	74 (29.1)	421 (26.7)	
Major genetic syndrome			0.11
Yes	30 (11.8)	133 (8.4)	
No	224 (88.2)	1445 (91.6)	
Other major anomaly			0.20
Yes	26 (10.2)	80 (5.1)	
No	228 (89.8)	1498 (94.9)	
Comprehensive parental postnatal support			0.06
Yes	237 (93.3)	1494 (94.7)	
No	17 (6.7)	84 (5.3)	
Any S1P preop feeding			0.25
Yes	121 (47.6)	950 (60.2)	
No	133 (52.4)	628 (39.8)	
Any S1P preop HM			0.25
Yes	98 (39.0)	803 (51.5)	
No	153 (61.0)	757 (48.5)	

Any S1P preop BF			0.34
Yes	18 (7.1)	288 (18.3)	
No	234 (92.9)	1,284 (81.7)	
S1P preop complications[c]			0.26
Yes	138 (54.3)	652 (41.3)	
No	116 (45.7)	926 (58.7)	
S1P postop complications[d]			0.57
Yes	229 (90.2)	1068 (67.7)	
No	25 (9.8)	510 (32.3)	
S1P postop ECMO			0.49
Yes	60 (23.9)	106 (6.7)	
No	191 (76.1)	1469 (93.3)	
Any major S1P postop procedure[e]			0.28
Yes	155 (61.0)	742 (47.0)	
No	99 (39.0)	836 (53.0)	
S1P postop time to full feeds (days)	25 (25)	14 (11)	-0.58

Abbreviations: ECMO = extracorporeal membrane oxygenation; HLHS = hypoplastic left heart syndrome; NPC-QIC = National Pediatric Cardiology Quality Improvement Collaborative; postop = postoperative; preop = preoperative; S1P = stage 1 palliation; S2P = stage 2 palliation; SDI = social deprivation index; SMD = standardized mean difference; SV = single ventricle; WAZ = weight-for-age z-score; ZCTA = zip code tabulation area.
Note: Percentages refer to the proportion of nonmissing data.
[a]An absolute SMD ≥0.10 is often considered indicative of differences between groups.
[b]SDI score range 0–100. Higher numbers indicate a higher level of social deprivation.
[c]S1P preop complications include arterial pH < 7.2, creatinine > 2, inotrope infusion at S1P, lactate > 3, mechanical ventilation to treat cardiorespiratory failure, necrotizing enterocolitis, preop neurological deficit, preop mechanical circulatory support, seizure during lifetime, sepsis, shock, or tracheostomy.
[d]S1P postoperative complications included arrhythmia requiring drug therapy or a pacemaker; necrotizing enterocolitis (treated medically or surgically); neurological deficit; paralyzed diaphragm; pleural effusion requiring drainage; pneumonia; pneumothorax requiring drainage or evacuation; respiratory insufficiency requiring reintubation; acute renal failure; seizure; sepsis; stroke; vocal cord dysfunction; or wound infection.
[e]S1P major postop procedures include bedside laryngoscopy to assess vocal cords, bronchoscopy, cardioversion, dialysis, diaphragm plication, fundoplication, gastrostomy tube, pericardiocentesis, thoracic duct ligation, tracheostomy.

preoperatively at S1P, and had greater incidence of S1P preoperative and postoperative complications.

Feeding outcomes: Elastic net logistic regression

Variables selected by elastic net logistic regression models for feeding outcomes at S1P discharge and at S2P can be found in Table 4.4, with variables that were significant in the models (ie, 95% CIs not including 1) visualized in Figure 4.1 and Figure 4.2. These variables were most frequently in the domains of (a) preoperative feeding practices, (b) demographics and SDoH, (c) feeding route at S1P discharge and S2P, and (d) clinical course. The variables with the strongest predictive value in the models (ie, highest variable importance score and 95% CIs not including 1) were also significant at $p<0.05$ in the unpenalized logistic regression sensitivity analysis, which can be found in Table 4.5.[20]

Table 4.4. Elastic Net Logistic Regression Models Identifying Variables Associated with Human Milk and Direct Breastfeeding at Stage 1 Palliation Discharge and at Stage 2 Palliation

At stage 1 palliation discharge				At stage 2 palliation			
Any human milk feeding				**Any human milk feeding**			
	OR	**95 % CI**	**VI score[a]**		**OR**	**95 % CI**	**VI score**
S1P length of stay (7 days)	0.89	**0.84–0.92**	100.00	S1P discharge feeding route[b]			
S1P preop feeding[b]				Any breastfeeding	4.11	**2.97–5.75**	100.00
Bottle with formula	0.36	**0.26–0.47**	55.51	Insurance: Private/Self	2.33	**1.64–3.08**	84.63
Any breastfeeding	2.02	**1.74–3.44**	55.49	S1P preop feeding[b]			
Bottle with human milk	1.19	1.00–1.83	25.07	Any breastfeeding	1.83	**1.30–2.71**	45.25
Insurance: Private/Self	1.91	**1.58–2.47**	54.97	Bottle with formula	0.66	**0.41–0.92**	24.42
S1P postop NEC	0.43	**0.28–0.55**	45.37	Bottle with human milk	0.78	**0.63–0.99**	16.44
Race: Black/African American	0.54	**0.38–0.65**	40.36	Race: Black/African American	0.57	**0.30–0.86**	40.29
Median income of residential ZCTA (unit = $10,000)	1.07	**1.03–1.15**	34.09	Age at S2P admission (7 days)	0.98	**0.96–1.00**	24.93
S1P postop days to enteral feeds	0.99	**0.96–1.00**	33.05	LAZ at S1P discharge	1.07	**1.01–1.16**	21.87
S1P postop days to full feeds	1.01	**1.00–1.03**	31.73	# of interstage procedures	0.89	0.71–1.00	20.39
S1P discharge feeding route[b]				Median income of residential ZCTA ($10,000)	1.04	1.00–1.10	19.41
G-tube	0.75	0.52–1.00	23.47	Parental 24-hour room in care before S1P discharge	0.59	**0.28–0.94**	17.41
Bottle	0.86	0.68–1.00	17.39	S1P postop laryngoscopy to	0.82	0.66–1.00	15.72
Need for S1P cardiac reoperation(s)	1.24	**1.00–1.82**	18.36	S1P preop instability	0.82	0.60–1.01	15.44
Diagnosis: Other SV	0.83	**0.66–0.98**	18.27	Fetal diagnosis	1.37	**1.02–2.05**	15.40
S1P postop instability	0.85	0.66–1.01	16.37	S1P preop NG nutrition type: Formula[b]	0.47	**0.16–1.00**	15.25
Born at the NPC-QIC center	0.86	**0.69–1.00**	16.23				
S1P preop NG nutrition type: Formula[b]	0.58	**0.27–0.87**	15.76				
Aortic obstruction at S1P	1.46	**1.05–2.48**	15.70				

Note: Additional variables selected for the model had VI scores <15 and CIs including 1. These variables were: S1P discharge feeding route (NG/NJ tube or Bottle); S1P preop feeding (NG trophic or NG > trophic); S1P preop NG nutrition type (Human milk + formula); S1P delayed chest closure; Interstage

Note: Additional variables selected for the model had VI scores <15 and CIs including 1. These variables were: S1P preop feeding (NG trophic or NG > trophic); S1P preop NG nutrition type (Human milk + formula or Human milk); Race: Another race/Multi-Race; S1P WAZ; Fetal diagnosis; S1P Intubation duration; SDI score of residential ZCTA; S1P postop laryngoscopy to assess vocal cords; S1P type; No S1P preop feeding: Clinical reasons; S1P preop instability; RUCA (Rural or Micropolitan); S1P preop enteral feeding; Major genetic syndrome; S1P preop NEC; S1P postop bronchoscopy; Hispanic or Latino/a ethnicity; Cross clamp during S1P; S1P: Reintubated within 48 hours; S1P: No CPB, CA, or CC; No S1P preop feeding: Institutional reasons; S1P discharge O2 saturation; Comprehensive parental postnatal support; Fortified feeding at S1P discharge; S1P discharge LAZ; S1P postop G-tube procedure; Preterm; No major S1P postop procedures; Weaned off inotropes/vasoactive meds within 5 days post S1P; Spontaneously breathing at S1P; S1P postop diaphragm plication; # of cardiac meds at S1P discharge; S1P discharge tricuspid regurgitation: Normal/mild; Age at S1P; Other major anomaly; Sex.

admission diagnosis (Cyanosis, Pneumonia, Respiratory distress, or Procedure for residual lesion); Comprehensive parental postnatal support; WAZ at S2P; S1P preop NEC; WAZ at S1P; Underwent any interstage procedure; S1P postop time to enteral feeds; S1P postop NEC; S1P CPB time; Need for cardiac reoperation(s) at S1P; S1P: ECMO in OR; S1P postop instability; Diagnosis: Other SV; S1P: reintubated within 48 hours; Fortified feeding at S1P discharge; RUCA (Micropolitan or Rural); # of interstage admissions; S1P cross clamp time; S1P postop time to full feeds; S1P discharge O2 saturation; No CPB, CA, or CC during S1P; Intubation duration; Major genetic syndrome; S2P aortic obstruction; S1P type (Norwood with BTT shunt or Other); S1P discharge TR: Normal/mild; S2P feeding route: Bottle; Other major anomaly; Preterm; S1P length of stay; Race: Another race/Multi-race.

Exclusive human milk feeding			
	OR	**95 % CI**	**VI score**
S1P discharge feeding route[b]			
Any breastfeeding	2.31	**1.62–3.31**	87.97
G-tube	0.36	**0.21–0.74**	65.43
Bottle feeding	0.50	**0.35–0.73**	47.29
NG/NJ tube	0.55	**0.40–0.82**	36.14
Insurance: Private/Self	1.55	**1.17–2.01**	51.95
S1P length of stay (7 days)	0.95	0.88–1.00	46.09
WAZ at S1P	1.34	**1.07–1.72**	45.51
S1P postop bronchoscopy	2.55	**1.17–5.66**	36.65
Other major anomaly	2.31	**1.05–4.27**	36.05
Spontaneously breathing at S1P	1.53	**1.00–2.57**	30.99
WAZ at birth	0.79	**0.60–0.95**	30.45
Fetal diagnosis	1.82	**1.08–3.53**	30.29
S1P postop days to full feeds	1.01	**1.00–1.03**	29.65

Exclusive human milk feeding			
	OR	**95 % CI**	**VI score**
Feeding route at S2P[b]			
Any breastfeeding	4.72	**2.81–8.53**	88.27
Bottle	0.45	**0.26–0.57**	87.32
NG/NJ tube	0.72	**0.38–0.97**	42.64
G-tube	0.81	0.42–1.01	27.45
Insurance: Private/Self	2.09	**1.39–3.41**	71.69
Race: Black/African American	0.57	**0.31–0.84**	45.21
Fortified feeding at S1P	0.45	**0.21–0.64**	42.41
Spontaneously breathing at S1P	1.57	**1.04–2.93**	39.45
No S1P preop feeding: Institutional reasons	1.70	**1.04–3.75**	38.98
Preterm <37 weeks	0.77	0.31–1.22	25.44
Born at the NPC-QIC center	1.19	1.00–1.70	23.73
ECMO in S1P operating room	1.85	0.74–4.62	20.71
WAZ at S2P	1.07	0.94–1.40	19.69

SDI score of residential ZCTA (10 points)[c]	0.94	0.88–1.00	29.26
TR at S1P discharge: Normal/mild	1.52	**1.00–2.85**	28.47
Cross clamp during S1P	1.40	0.99–1.95	27.43
Race: Another race/Multi-race	0.64	**0.34–0.97**	26.85
Median income of residential ZCTA ($10,000)	1.00	1.00–1.00	25.41
No S1P preop feeding: Institutional reasons	1.34	1.00–2.01	24.96
S1P delayed chest closure	0.82	0.63–1.02	21.03
Diagnosis: Other SV	0.87	0.64–1.04	19.27
Born at the NPC-QIC center	0.71	0.50–1.00	18.70
S1P preop feeding[b]			
Bottle with formula	0.70	0.44–1.11	18.57
Hispanic or Latino/a ethnicity	0.83	0.42–1.12	18.23
No major S1P postop procedures	1.13	0.86–1.54	16.14

Note: Additional variables selected for the model had VI scores <15 and CIs including 1. These variables were: S1P preop feeding (Any breastfeeding or Bottle with human milk); Major genetic syndrome; Race: Black/African American; Age at S1P; S1P: ECMO in OR; S1P preop instability; S1P preop enteral feeding; S1P postop instability; S1P weaned off inotropes/vasoactive meds within 5 days postop; S1P preop NEC.

Interstage admission: Wound infection/dehiscence[b]	0.61	**0.23–0.94**	18.71
Interstage procedure for residual lesion	0.65	**0.20–0.93**	18.19
SDI score of residential ZCTA (10 points)[c]	0.97	0.88–1.01	17.03
S1P discharge feeding route: NG/NJ tube[b]	1.12	0.95–1.63	16.61

Note: Additional variables selected for the model had VI scores <15 and CIs including 1. These variables were: Interstage admission diagnosis (Respiratory distress, GERD, Vomiting and diarrhea, Bloody stool, Pneumonia, Poor weight gain, or Infection); S1P postop: Diaphragm plication; LAZ at S1P discharge; WAZ at S1P discharge; S1P preop NEC; WAZ at S1P; S1P discharge aortic obstruction; S1P postop time to full feeds; S1P delayed chest closure; S2P oxygen saturation; S1P preop NG nutrition type; S1P length of stay; Other major anomaly; S1P preop feeding (Bottle with human milk, Bottle with formula, or NG/NJ tube); Need for cardiac reoperation(s) at S1P; RUCA (Rural or Micropolitan); Cross clamp during S1P; Parental 24-hour room in care before S1P discharge; Comprehensive parental postnatal support; S1P postop laryngoscopy to assess vocal cords; Aortic obstruction at S2P; S1P discharge tricuspid regurgitation: Normal/mild; S1P postop NEC; S1P postop: Fundoplication; Interstage admission(s) for a major adverse event; S1P: Weaned off inotropes/vasoactive meds within 5 days; Received preop enteral feeds; Fetal diagnosis; S2P oxygen saturation; S1P type; Median income of residential ZCTA; # of cardiac meds at S1P discharge; S1P postop bronchoscopy; Age at S1P; S1P CPB duration; Age at S2P admission; S1P preop instability; Sex; S1P postop instability; Diagnosis: Other SV; Hispanic or Latino/a ethnicity; Time to enteral feeds; Race: Another race/Multi-race; S1P discharge feeding route (G-tube or any breastfeeding).

Any direct breastfeeding			
	OR	**95 % CI**	**VI score**
S1P discharge feeding route[b]			
NG/NJ tube	0.37	**0.22–0.42**	99.53
G-tube	0.35	**0.12–0.64**	91.60
Bottle	0.69	**0.39–0.89**	48.34
S1P preop feeding[b]			
Any breastfeeding	3.02	**2.41–4.83**	86.29
Bottle with formula	0.51	**0.29–0.78**	43.71
Bottle with human milk	0.78	**0.54–1.00**	21.83
S1P length of stay (7 days)	0.93	**0.84–0.96**	75.61
S1P postop G-tube procedure	0.55	0.24–1.00	53.39
Median income of residential ZCTA ($10,000)	1.10	**1.04–1.20**	43.87
S1P postop ECMO	0.58	**0.23–0.81**	39.26
Fortified feeding at S1P	0.47	**0.27–0.67**	38.50
Age at S1P (days)	0.99	0.96–1.00	37.00
TR at S1P discharge: Normal/mild	0.75	**0.52–0.97**	25.96
S1P type: Norwood with BTT	0.77	**0.49–0.99**	24.41
S1P postop laryngoscopy to assess vocal cords	0.80	0.50–1.00	24.12
S1P preop enteral feeding	0.84	0.51–1.00	23.93
S1P preop instability	0.83	0.61–1.00	19.81
Insurance: Private/Self	1.20	**1.00–1.67**	18.49
RUCA: Rural	0.82	0.38–1.00	17.36
S1P need for cardiac reoperation(s)	1.20	1.00–1.85	16.94
WAZ at S1P discharge	1.08	1.00–1.30	16.51
LAZ at S1P discharge	1.04	0.97–1.15	15.27

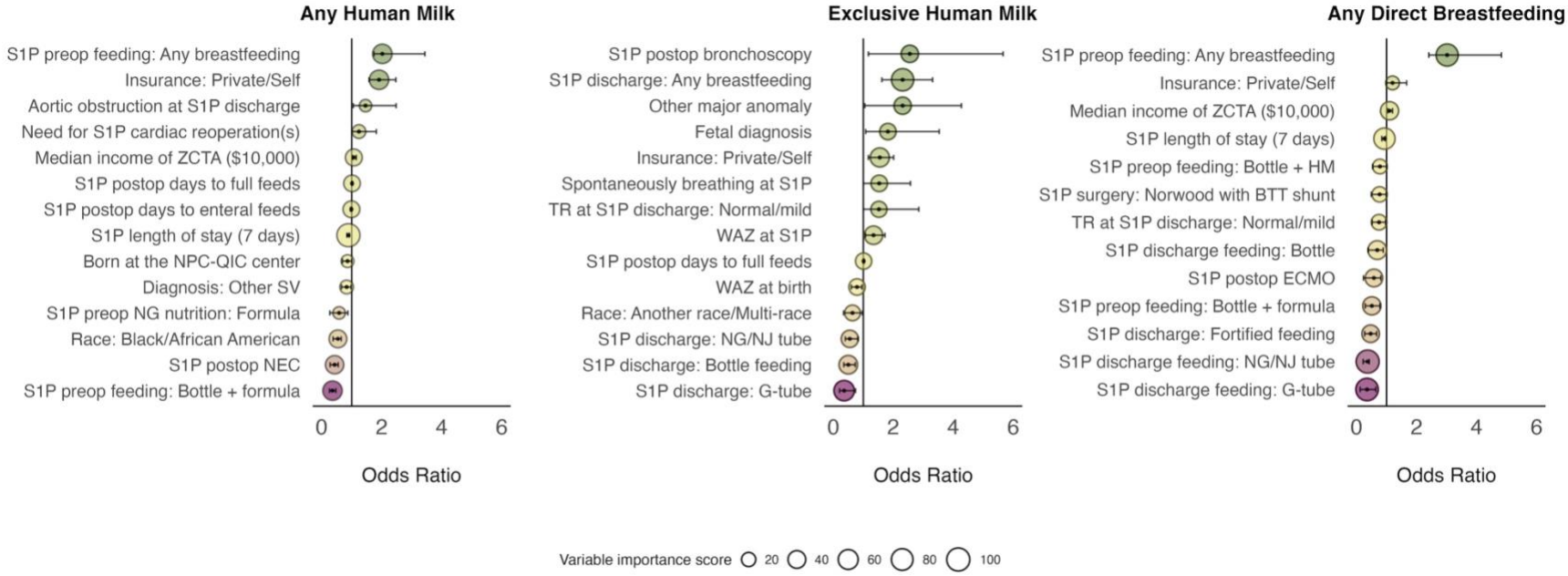
Any direct breastfeeding			
	OR	**95 % CI**	**VI score**
S1P discharge feeding route[b]			
Any breastfeeding	11.39	**8.28–21.18**	100.00
Feeding route at S2P[b]			
NG/NJ tube	0.14	**0.05–0.30**	80.92
Bottle	0.19	**0.07–0.40**	63.44
G-tube	0.18	**0.06–0.47**	63.03
S1P preop feeding[b]			
Any breastfeeding	2.09	**1.43–3.62**	29.97
Bottle with human milk	0.55	**0.32–0.82**	23.22
S1P delayed chest closure	1.92	**1.22–3.10**	27.21
S1P postop: Diaphragm plication	0.12	**0.04–0.29**	22.66
Spontaneously breathing at S1P	0.50	**0.27–0.78**	21.32
Major genetic syndrome	0.40	**0.18–0.67**	20.97
Insurance: Private/Self	1.50	**1.01–2.50**	19.05
S1P preop instability	0.68	**0.45–1.00**	16.01
Born at the NPC-QIC center	1.45	**1.02–2.18**	15.16

Note: Additional variables selected for the model had VI scores <15 and CIs including 1. These variables were: S1P discharge feeding route: G-tube; S1P preop feeding: NG trophic; RUCA (Micropolitan or Rural); S1P: reintubated within 48 hours; Preterm; LAZ at S1P discharge; Interstage admission diagnosis (GERD, Infection requiring IV antibiotics, Vomiting/diarrhea, Cyanosis, or Procedure for residual lesion); S1P discharge tricuspid regurgitation: Normal/mild; SDI score of residential ZCTA; LAZ at S2P; Weaned off inotropes/vasoactive meds within 5 days; S1P preop NG nutrition (Formula or Human milk); Parental 24-hour room in care before S1P discharge; Sex; Any major interstage procedure; S1P length of stay; S1P cross clamp time; S1P postop instability; S1P postop procedure for G-tube; # of interstage readmissions; WAZ at S2P; S1P postop time to full feeds; Race (Black/African American or Another Race/Multi-Race); Hispanic or Latino/a

Note: Additional variables selected for the model had VI scores <15 and CIs including 1. These variables were: S1P: No CPB, CA, or CC; # of cardiac meds at S1P discharge; S1P type: Other; S1P CPB time; Parental 24-hour room in care before S1P discharge; Sex; Fetal diagnosis; S1P delayed chest closure; S1P discharge O2 saturation; S1P postop diaphragm plication; Other major anomaly; Race: Black/African American; RUCA: Micropolitan; WAZ at S1P; Diagnosis: Other SV; Hispanic or Latino/a ethnicity; WAZ at birth. ethnicity; O2 saturation at S1P discharge; # of interstage admissions for adverse event; S1P type.

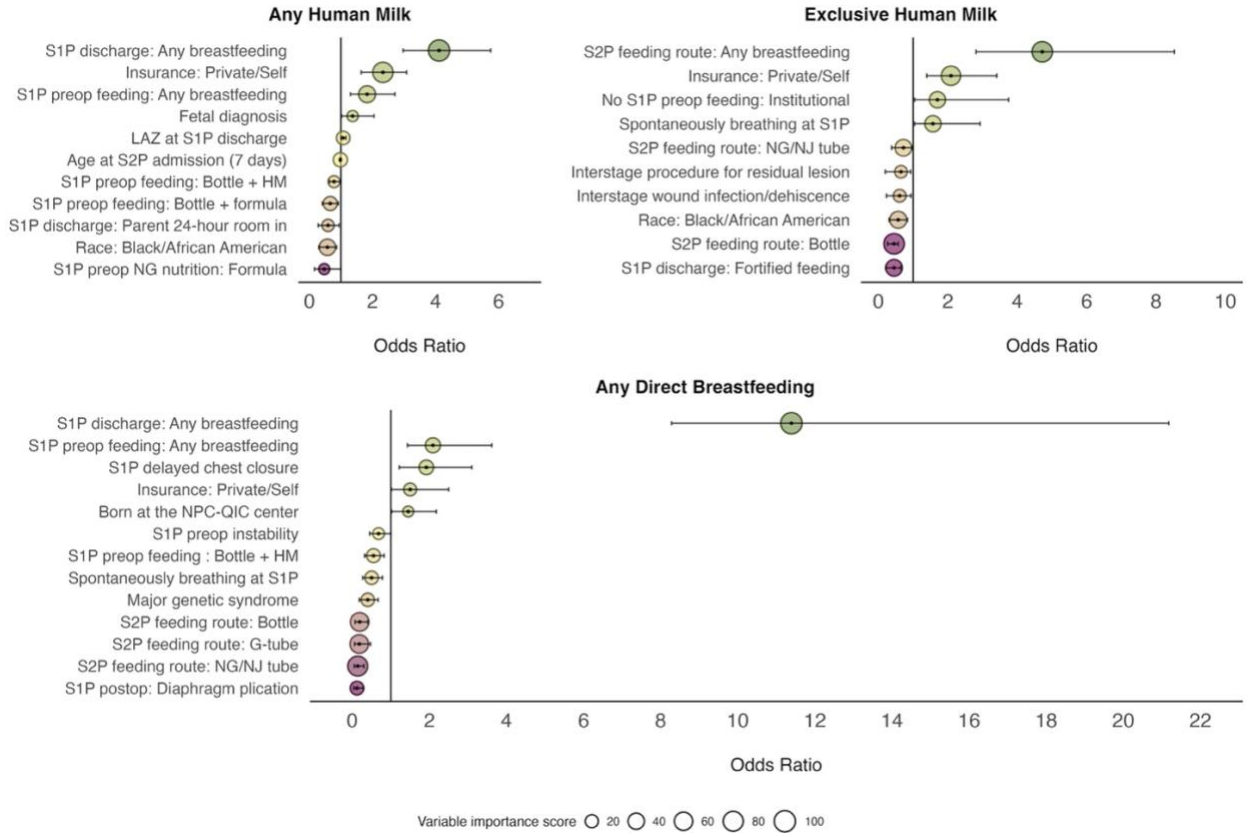
Abbreviations: BTT = Blalock–Thomas–Taussig; CA = circulatory arrest; CC = cross clamp; CI = confidence interval; CPB = cardiopulmonary bypass; ECMO = extracorporeal membrane oxygenation; G-tube = gastrostomy tube; GERD = gastroesophageal reflux disease; LAZ = length-for-age z-score; NEC = necrotizing enterocolitis; NG = nasogastric; NJ = nasojejunal; NPC-QIC = National Pediatric Cardiology Quality Improvement Collaborative; O2 = oxygen; OR = odds ratio; postop = postoperative; preop = preoperative; RUCA = rural-urban commuting area; S1P = stage 1 palliation; S2P = stage 2 palliation; SDI = social deprivation index; SV = single ventricle; VI = variable importance; WAZ = weight-for-age z-score; ZCTA = zip code tabulation area.
Notes: Reference groups: Insurance = government; Race = White.
Bold text in the 95% CI column indicates significant predictor.
[a]Variable importance score range = 0–100.
[b]No reference group.
[c]SDI score range, 0–100. Higher numbers indicate a higher level of social deprivation.
[d]Fortified feeding = a calorie goal of ≥ 22 kcal/oz.

Figure 4.1. Significant Predictors of Human Milk Feeding and Any Direct Breastfeeding at Stage 1 Palliation Discharge for Infants with Single Ventricle Congenital Heart Disease in the National Pediatric Cardiology Quality Improvement Collaborative Registry (2016–2012)



Abbreviations: BTT = Blalock–Thomas–Taussig; ECMO = extracorporeal membrane oxygenation; G-tube = gastrostomy tube; HM = human milk; NEC = necrotizing enterocolitis; NG = nasogastric; NJ = nasojejunal; NPC-QIC = National Pediatric Cardiology Quality Improvement Collaborative; postop = postoperative; preop = preoperative; S1P = stage 1 palliation; SV = single ventricle; TR = tricuspid regurgitation; WAZ = weight-for-age z-score; ZCTA = zip code tabulation area.
Notes: Analysis included elastic net logistic regression for each of 10 imputed data sets using the "MAMI" package in R to combine results and obtain bootstrap confidence intervals. Results are presented as odds ratios and 95% confidence intervals.
Reference groups are: Insurance = Government; Race = White.
There are no reference groups for S1P preop and S1P discharge feeding variables. These are treated as binary (yes/no).
Infants were considered to have fortified feeding if the recommended calorie goal at discharge was ≥ 22 kcal/oz.

Figure 4.2. Significant Predictors of Human Milk Feeding and Any Direct Breastfeeding at Stage 1 Palliation Discharge for Infants with Single Ventricle Congenital Heart Disease in the National Pediatric Cardiology Quality Improvement Collaborative Registry (2016–2012)



Abbreviations: G-tube = gastrostomy tube; HM = human milk; LAZ = length-for-age z-score; NG = nasogastric; NJ = nasojejunal; NPC-QIC = National Pediatric Cardiology Quality Improvement Collaborative; postop = postoperative; preop = preoperative; S1P = stage 1 palliation; S2P = stage 2 palliation.
Notes: Analysis included elastic net logistic regression for each of 10 imputed data sets using the "MAMI" package in R to combine results and obtain bootstrap confidence intervals. Results are presented as odds ratios and 95% confidence intervals. Reference groups are: Insurance = Government; Race = White.
There are no reference groups for S1P preop, S1P discharge, and S2P feeding variables. These are treated as binary (yes/no).
No S1P preop feeding: Institutional = no preoperative feeding due to institutional practice.
Infants were considered to have fortified feeding if the recommended calorie goal at discharge was ≥ 22 kcal/oz.

Table 4.5. Sensitivity Analysis Using Unpenalized Logistic Regression to Identify Variables Associated with Human Milk and Direct Breastfeeding at Stage 1 Palliation Discharge and at Stage 2 Palliation, Including Variables Retained in Final Elastic Net Regression Models

	At stage 1 palliation discharge								
	Any human milk feeding			Exclusive human milk feeding			Any direct breastfeeding		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Prenatal variables									
Fetal diagnosis	1.34	0.93–1.93	0.117	2.08	1.11–3.90	**0.023**	1.19	0.72–1.98	0.487
Characteristics at birth									
Born at the NPC-QIC center	0.79	0.61–1.02	0.072	0.66	0.46–0.95	**0.024**	–	–	–
Preterm (<37 weeks)	0.97	0.65–1.45	0.895	–	–	–	–	–	–
WAZ at birth	–	–	–	0.74	0.59–0.93	**0.009**	1.02	0.87–1.21	0.776
Diagnosis: Other SV	0.76	0.59–1.00	**0.047**	0.85	0.57–1.25	0.406	0.94	0.65–1.36	0.757
Major genetic syndrome	1.36	0.93–1.96	0.109	1.62	0.94–2.80	0.084	–	–	–
Other major anomaly	0.89	0.55–1.45	0.644	2.62	1.37–5.02	**0.004**	0.86	0.39–1.90	0.705
Sex: Female	1.03	0.82–1.30	0.770	–	–	–	0.88	0.64–1.20	0.409
Race									
Another race/Multi-race	1.13	0.77–1.65	0.538	0.60	0.30–1.19	0.140	0.85	0.51–1.42	0.532
Black/African American	0.47	0.34–0.66	**<0.001**	0.77	0.45–1.33	0.356	0.88	0.53–1.47	0.623
Hispanic or Latino/a ethnicity	0.78	0.56–1.09	0.146	0.83	0.46–1.48	0.521	1.18	0.75–1.86	0.480
Insurance: Private/Self	2.04	1.60–2.60	**<0.001**	1.60	1.11–2.30	**0.012**	1.24	0.89–1.72	0.197
Median income of residential ZCTA ($10,000)	1.12	1.03–1.21	**0.006**	0.89	0.80–1.00	**0.040**	1.11	1.04–1.18	**0.002**
SDI score of residential ZCTA (10 points)[b]	1.05	0.99–1.12	0.115	0.91	0.83–1.00	**0.050**	–	–	–
Rural-urban commuting area									
Micropolitan	0.79	0.54–1.16	0.230	–	–	–	0.85	0.49–1.49	0.576
Rural/Small town	0.75	0.49–1.14	0.176	–	–	–	0.60	0.32–1.13	0.115
Comprehensive parental postnatal support	0.76	0.45–1.27	0.295	–	–	–	–	–	–
S1P preoperative variables									
Preop enteral feeding	1.08	0.28–4.17	0.913	0.76	0.45–1.31	0.326	0.73	0.47–1.14	0.169
Preop feeding route and/or type[a]									

Any breastfeeding	2.84	1.94–4.15	**<0.001**	1.36	0.84–2.21	0.213	4.17	2.76–6.28	**<0.001**
Bottle with human milk	1.56	1.10–2.23	**0.013**	1.16	0.72–1.87	0.542	0.72	0.48–1.08	0.109
Bottle with formula	0.34	0.23–0.50	**<0.001**	0.68	0.34–1.34	0.265	0.40	0.22–0.74	**0.003**
NG trophic	2.82	0.78–10.13	0.112	–	–	–	–	–	–
Preop NG nutrition type[a]									
Human milk	0.46	0.12–1.81	0.267	–	–	–	–	–	–
Formula	0.20	0.04–1.02	0.052	–	–	–	–	–	–
Human milk + formula	0.48	0.09–2.51	0.384	–	–	–	–	–	–
No preop feeding: Clinical reasons	1.71	0.47–6.30	0.417	–	–	–	–	–	–
No preop feeding: Institutional reasons	1.72	0.47–6.29	0.410	1.38	0.82–2.34	0.229	–	–	–
Preop instability	0.83	0.65–1.07	0.151	1.32	0.91–1.92	0.140	0.77	0.56–1.07	0.120
Preop NEC	1.93	0.79–4.73	0.151	0.44	0.06–3.57	0.446	–	–	–
S1P operative variables									
Age at S1P (days)	1.00	0.99–1.01	0.835	1.00	0.97–1.02	0.832	0.98	0.95–1.01	0.115
WAZ at S1P	1.13	0.99–1.29	0.068	1.46	1.13–1.88	**0.003**	1.05	0.82–1.35	0.683
Spontaneously breathing at S1P	1.10	0.81–1.48	0.538	1.65	1.00–2.70	**0.048**	–	–	–
Surgery/Intervention type									
Hybrid Norwood	0.86	0.37–1.99	0.719	–	–	–	1.01	0.35–2.93	0.990
Norwood with BTT shunt	0.79	0.59–1.04	0.094	–	–	–	0.64	0.43–0.95	**0.028**
Other	0.91	0.61–1.38	0.666	–	–	–	1.29	0.77–2.16	0.341
Utilized cross clamp	0.69	0.41–1.16	0.158	1.54	0.88–2.69	0.130	–	–	–
No CPB, CA, or cross clamp	0.66	0.27–1.59	0.354	–	–	–	1.49	0.55–4.06	0.434
CPB duration (10 minutes)	–	–	–	–	–	–	0.99	0.97–1.03	0.737
ECMO in the operating room	–	–	–	0.48	0.10–2.21	0.345	–	–	–
S1P postoperative variables									
Delayed chest closure	–	–	–	0.83	0.57–1.20	0.317	1.20	0.84–1.71	0.316
S1P intubation duration (days)	0.98	0.97–1.00	0.119	–	–	–	–	–	–
Postop: Reintubated within 48 hours	0.81	0.58–1.15	0.239	–	–	–	–	–	–
Need for S1P cardiac reoperation(s)	1.48	1.06–2.06	**0.020**	–	–	–	1.45	0.94–2.24	0.091
Postop ECMO	–		–	–	–	–	0.34	0.15–0.80	**0.014**
Postop instability	0.79	0.61–1.04	0.096	0.84	0.58–1.23	0.371	–	–	–
Postop NEC	0.39	0.27–0.56	**<0.001**	–	–	–	–	–	–
Postop bronchoscopy	1.42	0.81–2.49	0.218	2.93	1.37–6.25	**0.005**	–	–	–

Postop laryngoscopy to assess vocal cords	0.82	0.59–1.14	0.229	–	–	–	0.72	0.50–1.05	0.085
Postop diaphragm plication	0.83	0.42–1.61	0.576	–	–	–	1.67	0.64–4.40	0.298
Postop G-tube procedure	0.92	0.51–1.66	0.777	–	–	–	0.51	0.18–1.48	0.214
No postop procedures	1.05	0.73–1.49	0.800	1.15	0.77–1.71	0.505	–	–	–
Postop time to enteral feeds (days)	0.97	0.94–1.00	0.051	–	–	–	–	–	–
Postop time to full feeds (days)	1.02	1.01–1.03	**0.002**	1.02	1.00–1.03	**0.029**	–	–	–
Weaned inotropes/vasoactive meds within 5 days	0.89	0.69–1.16	0.401	1.03	0.71–1.51	0.860	–	–	–
S1P discharge variables									
WAZ at discharge	–	–	–	–	–	–	1.06	0.82–1.38	0.642
LAZ at discharge	0.96	0.88–1.05	0.412	–	–	–	1.04	0.90–1.19	0.609
Discharge feeding route[a]									
Any breastfeeding	–	–	–	2.32	1.55–3.49	**<0.001**	–	–	–
Bottle feeding	0.76	0.59–0.98	**0.037**	0.43	0.28–0.65	**<0.001**	0.44	0.30–0.64	**<0.001**
NG/NJ tube	–	–	–	0.47	0.31–0.72	**<0.001**	0.25	0.17–0.36	**<0.001**
G-tube	0.68	0.38–1.21	0.189	0.29	0.15–0.56	**<0.001**	0.20	0.07–0.57	**0.002**
Fortified feeding at discharge[c]	0.82	0.52–1.30	0.400	–	–	–	0.40	0.25–0.64	**<0.001**
Aortic obstruction at discharge	1.93	0.88–4.24	0.101	–	–	–	–	–	–
TR at discharge: Normal/mild	0.93	0.69–1.26	0.640	1.65	1.00–2.72	**0.049**	0.59	0.40–0.87	**0.007**
Oxygen saturation at discharge	1.01	0.99–1.03	0.312	–	–	–	0.99	0.96–1.01	0.276
# of cardiac meds at discharge	0.97	0.85–1.10	0.645	–	–	–	0.91	0.76–1.08	0.271
Parental 24-hour room in care before discharge	–	–	–	–	–	–	1.54	0.70–3.37	0.283
S1P length of stay (7 days)	0.86	0.83–0.90	**<0.001**	0.95	0.89–1.02	0.126	0.90	0.84–0.96	**0.001**

	At stage 2 palliation								
	Any human milk feeding			**Exclusive human milk feeding**			**Any direct breastfeeding**		
	OR	**95% CI**	**p value**	**OR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Prenatal variables									
Fetal diagnosis	1.56	0.99–2.46	0.056	0.77	0.30–1.95	0.576	–	–	–
Characteristics at birth									
Born at the NPC-QIC center	–	–	–	1.55	0.93–2.59	0.095	1.56	0.96–2.53	0.070
Preterm (<37 weeks)	0.82	0.46–1.47	0.505	0.60	0.18–1.99	0.404	0.41	0.14–1.21	0.105

WAZ at birth	–	–	–	–	–	–	–	–	–
Diagnosis: Other SV	1.29	0.93–1.79	0.129	1.13	0.65–1.99	0.661	–	–	–
Major genetic syndrome	0.75	0.45–1.24	0.259	–	–	–	0.29	0.09–0.93	**0.037**
Other major anomaly	0.83	0.42–1.64	0.591	0.58	0.12–2.86	0.494	–	–	–
Sex: Female	–	–	–	0.98	0.64–1.52	0.936	1.40	0.88–2.24	0.159
Race									
Another race/Multi-race	1.01	0.65–1.56	0.980	0.74	0.31–1.81	0.511	0.82	0.34–1.98	0.661
Black/African American	0.53	0.32–0.87	**0.013**	0.37	0.12–1.16	0.087	0.72	0.33–1.59	0.420
Hispanic or Latino/a ethnicity	–	–	–	1.24	0.58–2.67	0.579	0.78	0.36–1.67	0.523
Insurance: Private/Self	2.50	1.87–3.34	**<0.001**	2.67	1.58–4.54	**<0.001**	1.60	0.97–2.66	0.068
Median income of residential ZCTA ($10,000)	1.00	1.00–1.00	0.174	0.93	0.78–1.11	0.412	–	–	–
SDI score of residential ZCTA (10 points)[b]	–	–	–	0.92	0.78–1.08	0.304	1.08	0.99–1.18	0.072
Rural-urban commuting area									
Micropolitan	1.29	0.83–2.02	0.259	1.08	0.51–2.31	0.834	2.13	1.08–4.17	**0.028**
Rural/Small town	1.06	0.59–1.89	0.853	0.63	0.26–1.52	0.298	0.74	0.30–1.86	0.526
Comprehensive parental postnatal support	0.57	0.31–1.04	0.067	0.61	0.21–1.74	0.353	–	–	–
S1P preoperative variables									
Preop feeding route and/or type[a]									
Any breastfeeding	2.04	1.43–2.91	**<0.001**	–	–	–	2.29	1.38–3.80	**0.001**
Bottle with human milk	0.70	0.52–0.94	**0.018**	1.18	0.54–2.59	0.667	0.47	0.27–0.79	**0.005**
Bottle with formula	0.59	0.39–0.91	**0.017**	0.85	0.39–1.87	0.690	–	–	–
NG trophic	0.28	0.02–3.70	0.333	–	–	–	0.71	0.11–4.75	0.723
NG > trophic	0.38	0.03–5.03	0.461	1.00	0.15–6.81	0.999	–	–	–
Preop NG nutrition type[a]									
Human milk	2.81	0.20–38.64	0.437	1.36	0.48–3.87	0.555	0.87	0.14–5.49	0.883
Formula	0.80	0.04–15.09	0.880	0.00	0–Inf	0.989	0.22	0.01–4.48	0.325
Human milk + formula	1.54	0.08–30.23	0.776	0.01	0–Inf	0.993	1.50	0.16–13.91	0.722
No preop enteral feeding: Clinical reasons	–	–	–	0.83	0.39–1.78	0.634	–	–	–
No preop enteral feeding: Institutional reasons	–	–	–	2.57	0.98–6.72	0.054	–	–	–
S1P preop instability	0.77	0.57–1.02	0.071	1.20	0.74–1.95	0.448	0.60	0.36–1.02	0.057

Preop NEC	2.48	0.81–7.58	0.109	0.00	0–Inf	0.991	–	–	–
S1P operative variables									
Age at S1P (days)	–	–	–	0.99	0.96–1.03	0.657	–	–	–
WAZ at S1P	1.13	0.94–1.35	0.190	1.15	0.80–1.67	0.446	1.06	0.81–1.39	0.687
Spontaneously breathing at S1P	–	–	–	2.28	0.91–5.69	0.076	0.40	0.22–0.73	**0.003**
Surgery/Intervention type									
Hybrid Norwood	1.38	0.42–4.55	0.599	0.77	0.11–5.45	0.789	0.96	0.23–3.90	0.952
Norwood with BTT shunt	0.90	0.64–1.25	0.523	1.07	0.58–1.97	0.817	0.83	0.49–1.42	0.494
Other	0.77	0.46–1.27	0.301	1.14	0.49–2.63	0.765	0.68	0.31–1.50	0.343
Utilized cross clamp	–	–	–	1.22	0.42–3.50	0.708	–	–	–
No CPB, CA, or cross clamp	0.62	0.22–1.75	0.369	–	–	–	–	–	–
CPB duration (10 minutes)	0.97	0.94–1.00	0.087	1.00	0.95–1.04	0.831	–	–	–
Cross clamp duration (10 minutes)	1.02	0.97–1.08	0.399	–	–	–	1.03	0.96–1.10	0.465
ECMO in the operating room	2.21	0.92–5.31	0.078	2.97	0.81–10.91	0.100	–	–	–
S1P postoperative variables									
Delayed chest closure	1.41	1.03–1.94	**0.034**	0.79	0.45–1.38	0.398	2.17	1.23–3.83	**0.007**
Intubation duration (days)	0.97	0.95–1.00	0.066	–	–	–	–	–	–
Reintubated within 48 hours	0.76	0.49–1.17	0.212	–	–	–	0.56	0.24–1.30	0.175
Need for cardiac reoperation(s)	1.23	0.82–1.84	0.326	1.25	0.67–2.35	0.478	–	–	–
Postop instability	0.88	0.64–1.21	0.442	1.02	0.59–1.78	0.930	0.95	0.58–1.54	0.826
Postop NEC	0.66	0.40–1.10	0.113	0.72	0.30–1.73	0.459	–	–	–
Postop bronchoscopy	–	–	–	0.93	0.24–3.65	0.912	–	–	–
Postop laryngoscopy to assess vocal cords	0.78	0.56–1.09	0.148	0.87	0.44–1.75	0.698	–	–	–
Postop diaphragm plication	–	–	–	0.03	0–Inf	0.989	0.00	0–Inf	0.985
Postop fundoplication	–	–	–	0.69	0.07–6.74	0.739	–	–	–
Postop G-tube procedure	–	–	–	–	–	–	1.10	0.20–5.94	0.916
Postop time to enteral feeds (days)	1.03	1.00–1.06	0.100	0.99	0.95–1.03	0.703	–	–	–
Postop time to full feeds (days)	1.01	0.99–1.02	0.438	0.99	0.96–1.03	0.775	1.01	0.99–1.04	0.209
Weaned inotropes/vasoactive meds within 5 days	–	–	–	0.78	0.46–1.35	0.376	–	–	–
S1P discharge variables									
WAZ at discharge	–	–	–	1.03	0.63–1.69	0.889	–	–	–
LAZ at discharge	1.08	0.95–1.24	0.234	–	–	–	1.05	0.89–1.25	0.536

Discharge feeding route[a]									
Any breastfeeding	4.89	3.30–7.27	**<0.001**	0.89	0.47–1.71	0.731	13.86	8.50–22.6	**<0.001**
Bottle feeding	0.81	0.57–1.16	0.248	–	–	–	–	–	–
NG/NJ tube	1.25	0.92–1.70	0.155	1.50	0.82–2.76	0.186	–	–	–
G-tube	–	–	–	1.12	0.38–3.36	0.835	0.69	0.17–2.83	0.608
Fortified feeding at discharge[c]	1.45	0.85–2.46	0.174	0.34	0.17–0.68	**0.002**	–	–	–
Aortic obstruction at discharge	–	–	–	1.71	0.39–7.55	0.469	–	–	–
TR at discharge: Normal/mild	1.20	0.82–1.76	0.337	1.36	0.66–2.78	0.397	1.68	0.87–3.24	0.123
Oxygen saturation at discharge	1.01	0.99–1.04	0.352	1.02	0.97–1.07	0.386	1.01	0.96–1.05	0.750
# of cardiac meds at discharge	–	–	–	1.01	0.72–1.42	0.958	1.30	0.80–2.13	0.292
Parental 24-hour room in care before discharge	0.48	0.22–1.04	0.063	0.71	0.21–2.42	0.578	0.46	0.16–1.37	0.164
S1P length of stay (7 days)	1.01	0.96–1.06	0.729	0.99	0.88–1.12	0.850	0.96	0.87–1.07	0.488
Interstage variables									
# of interstage readmissions	1.09	0.73–1.64	0.667	–	–	–	0.94	0.66–1.33	0.725
Interstage admission diagnosis[a]									
Bloody stool	–	–	–	1.34	0.52–3.43	0.541	–	–	–
Cyanosis	1.56	0.98–2.47	0.061	–	–	–	1.58	0.78–3.20	0.203
GERD	–	–	–	0.01	0–Inf	0.991	0.00	0–Inf	0.987
Infection requiring IV antibiotics				53.48	0–Inf	0.989	0.00	0–Inf	0.989
Pneumonia	0.61	0.25–1.48	0.271	0.51	0.11–2.41	0.395	–	–	–
Procedure for residual lesion	1.81	0.71–4.62	0.212	0.24	0.02–2.67	0.238	4.55	1.24–16.74	**0.023**
Respiratory distress	0.61	0.29–1.26	0.180	0.45	0.08–2.65	0.373	–	–	–
Vomiting/Diarrhea				0.74	0.28–1.98	0.549	0.71	0.20–2.52	0.592
Weight gain	–	–	–	0.76	0.22–2.58	0.654	–	–	–
Wound infection/dehiscence	–	–	–	0.23	0.04–1.45	0.115	–	–	–
Underwent any interstage procedure	0.82	0.50–1.36	0.440	–	–	–	0.76	0.37–1.58	0.467
# of interstage procedures	0.78	0.49–1.24	0.288	–	–	–	–	–	–
Admission for a major adverse event	–	–	–	0.05	0–Inf	0.992	0.90	0.12–6.82	0.915
# of major adverse events									
S2P preoperative variables									
Age at S2P (days)	1.00	0.99–1.00	0.087	1.00	0.99–1.01	0.919	–	–	–
WAZ at S2P	0.87	0.75–1.00	**0.044**	1.15	0.84–1.57	0.382	–	–	–
LAZ at S2P	–	–	–	1.03	0.84–1.27	0.752	1.08	0.91–1.29	0.393

Feeding route at S2P[a]									
Any breastfeeding	–	–	–	5.69	2.73–11.83	**<0.001**	–	–	–
Bottle feeding	0.86	0.62–1.18	0.341	0.22	0.09–0.56	**0.003**	0.10	0.05–0.21	**<0.001**
NG/NJ tube				0.36	0.14–0.90	**0.031**	0.07	0.03–0.17	**<0.001**
G-tube	–	–	–	0.41	0.13–1.31	0.132	0.08	0.02–0.28	**<0.001**
Aortic obstruction at S2P	0.85	0.41–1.78	0.661	1.19	0.32–4.51	0.784	–	–	–
Oxygen saturation at S2P	–	–	–	0.99	0.95–1.03	0.552	–	–	–

Abbreviations: BTT = Blalock–Thomas–Taussig; CA = circulatory arrest; CI = confidence interval; CPB = cardiopulmonary bypass; ECMO = extracorporeal membrane oxygenation; G-tube = gastrostomy tube; GERD = gastroesophageal reflux disease; HM = human milk; IV = intravenous; LAZ = length-for-age z-score; NEC = necrotizing enterocolitis; NG = nasogastric; NJ = nasojejunal; NPC-QIC = National Pediatric Cardiology Quality Improvement Collaborative; O2 = oxygen; OR = odds ratio; postop = postoperative; preop = preoperative; RUCA = rural-urban commuting area; S1P = stage 1 palliation; S2P = stage 2 palliation; SDI = social deprivation index; SV = single ventricle; WAZ = weight-for-age z-score; ZCTA = zip code tabulation area.

Notes: Reference groups: Insurance = government; Race = White.

[a]No reference group.

[b]SDI score range, 0–100. Higher numbers indicate a higher level of social deprivation.

[c]Fortified feeding = a calorie goal of ≥ 22 kcal/oz.

Preoperative feeding practices. Preoperative route and type of nutrition were significantly associated with later HM/BF outcomes. Any preoperative BF was associated with increased odds of any HM (OR=2.02, 95% CI=1.74–3.44) and any BF (3.02, 2.41–4.83) at S1P discharge, with similar results at S2P. In contrast, preoperative bottle feeding, whether formula or HM, was negatively associated with HM/BF at both time points.

Demographics and SDoH. Demographics and SDoH were frequently significant in the models with race, insurance type, and median income of residential ZCTA significant predictors of HM/BF practices. Private/self insurance was associated with increased odds of any HM (1.91, 1.58–2.47), exclusive HM (1.55, 1.17–2.01), and any BF (1.20, 1.00–1.67) at S1P discharge and, with greater magnitude of effect size for all feeding outcomes, at S2P. Black/African American infants had lower odds of any HM (0.54, 0.38–0.65), but not any BF, at S1P discharge and at S2P (0.57, 0.30–0.86), compared to White infants.

Feeding route at S1P discharge and S2P. The route of feeding at S1P discharge and at S2P (ie, direct BF, bottle, or feeding tube) was also associated with HM/BF outcomes. Any direct BF at S1P discharge was positively associated with any HM (4.11, 2.97–5.75) and any direct BF (11.39, 8.28–21.18) at the subsequent S2P. Bottle feeding and tube feeding were associated with lower odds of HM/BF at both time points (eg, infants who were bottle feeding at S2P had 81% lower odds of any direct BF at the same S2P time point) .

Clinical course. Variables related to an infant's clinical course were significant in the models, but tended to have lower variable importance scores than preoperative feeding, demographics/SDoH, or feeding route factors (see Table 4.4). Length of stay during the S1P hospitalization was the exception, with each additional 7 days inpatient associated with 11% lower odds of any HM feeding (0.89, 0.84–0.92) and 7% lower odds of any direct BF (0.93, 0.84–0.96) at S1P discharge. Interstage clinical course variables were not frequently strong predictors.

Feeding outcomes: Institutional site

Odds ratios and 95% CIs for each feeding outcome varied among NPC-QIC sites, as can be seen in Figure 4.3. Likelihood ratio tests revealed that complete case models including NPC-QIC site were a better fit than those including only the variables retained in the elastic net logistic regression models at S1P discharge ($p<0.001$ for all feeding outcomes). At S2P, adding clinical site improved the model for exclusive HM feeding ($p<0.001$) but not for any HM feeding ($p=0.12$) or any direct BF ($p=0.28$).

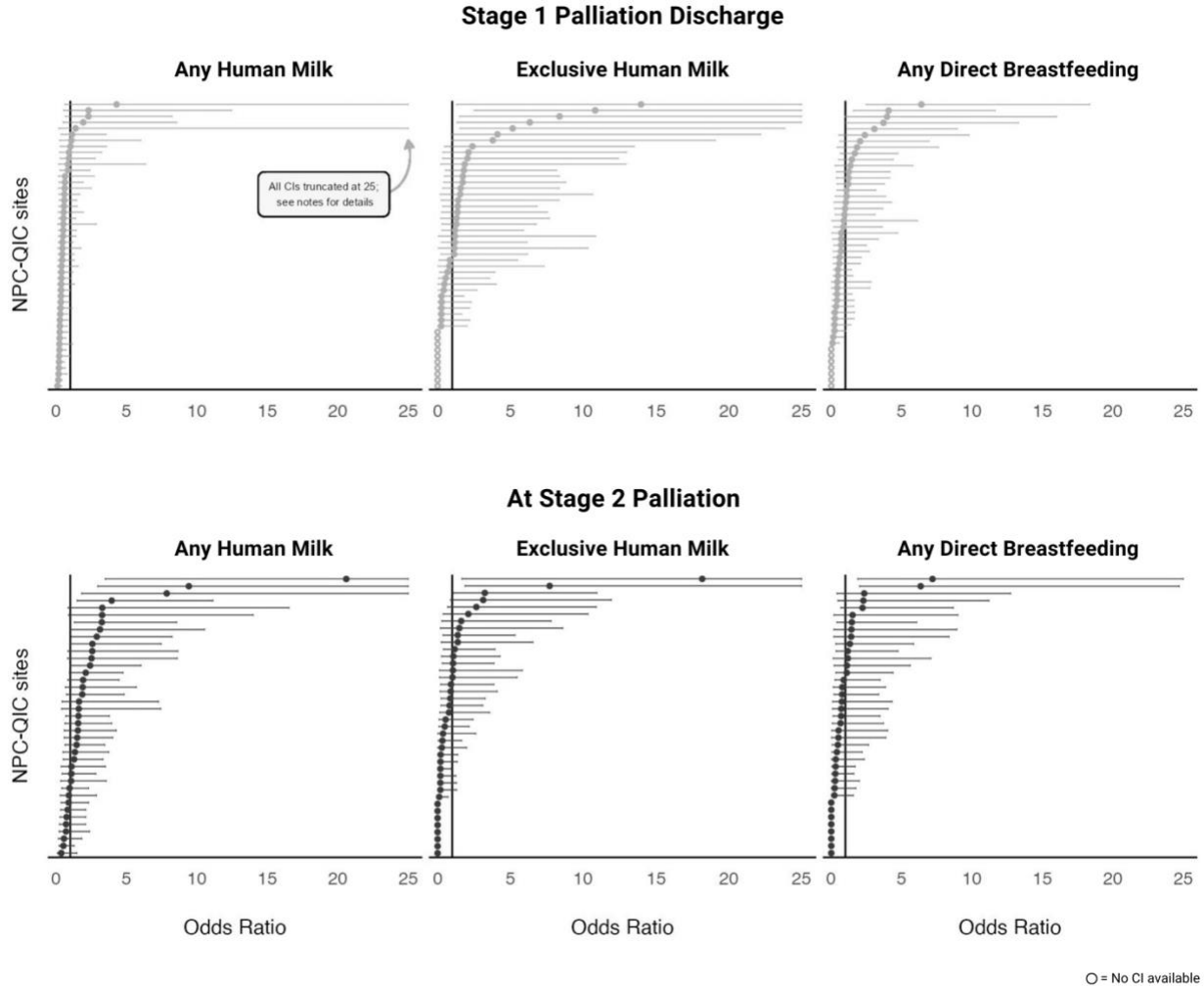
Discussion

In this national, multisite analysis, we identified factors that were significantly associated with HM feeding and direct BF for infants with SV CHD at S1P discharge and at S2P. To our knowledge, this is the first study to examine predictors of HM and BF practices for infants with CHD of any type, and our findings highlight areas of focus for future research and modifiable targets for practice improvement.

Preoperative feeding practices

For infants in our sample, preoperative feeding practices were strongly associated with later HM/BF outcomes at both S1P discharge and S2P. It is not altogether surprising that any preoperative BF was predictive of continued BF at later time points, as evidence from preterm populations supports a theory of feeding imprinting in which an infant's earliest oral feeding experience is foundational to later BF success.[38–40] However, the S1P preoperative time is usually short (ie, median 6 days[1]) and infants with SV CHD may experience a complex clinical course following a high-risk neonatal palliation. Common complications include cardiorespiratory instability and considerable time npo,[4] with a hospital stay of (mean) 7 weeks further interfering with the typical trajectory of direct BF establishment. Given these obstacles, our finding that relatively brief preoperative BF experiences may have lasting impact on future HM and BF outcomes is of potential value for clinical intervention.

Figure 4.3. Adjusted Odds Ratios and 95% Confidence Intervals for Human Milk Feeding and Any Direct Breastfeeding for National Pediatric Cardiology Quality Improvement Collaborative Sites, at Stage 1 Palliation Discharge and At Stage 2 Palliation



Abbreviations: CI = confidence interval; NPC-QIC = National Pediatric Cardiology Quality Improvement Project
Notes: Analysis included logistic regression on complete case data adjusted for race and insurance type.
Results are presented as odds ratios and 95% CIs.
Only NPC-QIC sites in the top 3 quartiles (n>10) are included.
The reference group for each analysis was selected to be a site with an average size and prevalence of the feeding outcome of interest.
Truncated upper CIs at stage 1 palliation discharge are (from top): Any human milk = 86.93, 30.24; Exclusive human milk = 145.81, 58.82, 52.67, 37.04.
Upper CIs at stage 2 palliation are (from top): Any human milk = 397.16, 55.53, 37.01; Exclusive human milk = 210.37, 34.12; Any direct breastfeeding = 32.04.

In contrast, preoperative bottle feeding – whether with HM or formula – predicted significantly lower odds not only of direct BF, but also of any HM feeding at S1P discharge and at the S2P time point. This result is striking, as parents of hospitalized neonates have reported clinical support for HM feeding via bottle or feeding tube, but not for direct BF.[19,41] Milk expression is burdensome, and parents have described difficulty maintaining extended HM expression given their child's significant medical needs.[19] Perceived and actual milk insufficiency have also been negatively associated with HM duration,[42] and early infant/parent separation with limited opportunities for practices known to support HM volume (eg, skin-to-skin contact between the infant and the lactating parent [43]) may also play a role.

Our findings suggest that the preoperative time may provide a window of opportunity in which to set the stage for the future nutrition of infants with SV CHD. Support of HM expression without concurrent support for direct BF could contribute to early HM weaning in this population. Early HM weaning is a concern, as only 37.1% of infants with SV CHD receive any HM feeding at S2P (~4.8 months old),[1] compared to the U.S. average of 55.8% at 6 months old.[44] Increased exposure to the personalized[21,45] benefits[6,7,11,21] of HM and BF may be particularly crucial for these vulnerable infants, and clinically-appropriate preoperative support for direct BF is a modifiable target for improvement [21] with potential for tremendous positive impact.

Demographics and SDoH

Variables related to demographics and SDoH were significant in all models. Economic indicators appeared most often, with private/self-pay insurance predictive of all HM/BF outcomes and higher ZCTA median income associated with significantly increased odds of HM/BF at S1P discharge. These findings align with previous studies[13,46–49] linking economic status with HM outcomes.

Black and African American infants had lower odds of HM at both time points, which is consistent with previous US studies,[13,14,47] although economic status, parental education, and clinical

practices may mediate the relationship between race and HM/BF.[13,46] In our multistep model selection process, we found that both socioeconomic indicators and Black race were strong predictors of HM/BF; however, mediation analysis was beyond the scope of this study.

Our findings highlight significant health disparities related to demographics and SDoH for infants with SV CHD, in which not all families have access to resources needed to establish and maintain HM feeding and BF. Reasons for these disparities range from the structural to the individual, and may include a lack of national or local policy support for HM and BF,[50] hospital quality,[21] financial and family strain due to a lengthy hospital stay,[48] low social support/no family history of HM/BF,[51] misconceptions about HM/BF,[51] low parental self-efficacy for HM/BF,[51] generational trauma related to direct BF,[51,52] structural racism,[53] and healthcare team implicit bias.[53] Unfortunately, evidence about the lactation-related experiences and needs of racially, culturally, and economically diverse families of infants with critical CHD is currently lacking,[19] and future research in this area is urgently needed to inform family-centered care.

On a clinical level, those caring for infants with SV CHD must address individual and institutional bias that could contribute to these infant feeding disparities. For example, Thomas's[53] qualitative investigation documents consistent, race-based discrimination by those providing lactation care, with providers consciously and unconsciously offering patients of color lower quality care and less frequent support. While the low HM and BF rates for infants with SV CHD signify a critical need for improved feeding support for all infants, healthcare systems should intentionally implement interventions that are effective in facilitating HM feeding and direct BF for Black families and those experiencing economic challenges. Evidence-based interventions could include community peer counselors,[48,54,55] comprehensive institutional practice change,[56] financial support for lactation-related hospital costs (eg, breast pump supplies; transportation and parking; childcare),[48] or conditional cash transfers (ie, financial incentives for HM/BF).[21] Healthcare team lactation-specific training should address bias and

racism, and future research should investigate the effectiveness of such training.

Feeding route at S1P discharge and at S2P

The route of feeding was significantly associated with nutrition type. Interestingly, infants directly BF at S1P discharge or at S2P were more likely to receive exclusive HM at the same time point. These BF infants may have experienced a more stable clinical course, with lower concern about weight gain or volume overload resulting in decreased recommendation for formula fortification. Alternatively, early development of the oral skills necessary for direct BF and/or an increased exposure to the immunological,[45,57] cardiorespiratory,[58] neurodevelopmental,[59,60] and stress reducing[61,62] benefits of direct BF could positively impact the infant's clinical course in ways that are not yet fully understood.

It is unsurprising that tube feeding was associated with lower odds of both exclusive HM feeding and any BF, as the existence of a feeding tube implies oral feeding problems or a concern about achieving prescribed weight gain goals with consequent fortification. Bottle feeding at S1P discharge and at S2P was similarly associated with lower odds of these feeding outcomes. This finding is less intuitive, as a recent study[19] revealed that 90% of breastfed infants undergoing neonatal surgery for CHD used a bottle at some point, and providers often recommend that infants with SV CHD alternate between direct BF and bottles of HM or formula fortified with extra nutrients. It is possible that balancing multiple methods of feeding is burdensome for the lactating parent, particularly if the parent engages in extended HM expression to support fortified bottle feeding.[19] However, more evidence is needed to clarify longitudinal[63] patterns of feeding for infants with SV CHD, as granular feeding practices are not well understood.

Clinical course

A longer S1P length of stay was associated with lower odds of HM/BF at S1P discharge. Longer hospitalization could be considered a surrogate for a complicated clinical course, and these lower odds

could reflect a lower physiological capability for feeding. Additionally, the environment of the ICU is a documented barrier to HM expression and BF establishment,[4,64] with maternal biomarkers[65,66], psychological stress,[67] and sleep interruptions[68] associated with delayed secretory activation and reduced milk volume.

Additional factors related to an infant's clinical course were significant in the models but were not as strongly predictive of feeding outcomes. Infants undergoing a Norwood procedure with a Blalock–Thomas–Taussig (BTT) shunt had 23% lower odds of direct BF at S1P discharge compared to a Norwood with Sano shunt, which echoes previous findings that the Norwood/BTT is associated with greater postoperative complications.[69] It is important to note that clinical course, or an infant's relative "sickness," did not appear to be the primary driver of HM/BF outcomes in our sample, which aligns with qualitative[19] and quantitative[70] findings that postoperative instability does not consistently predict delayed oral feeding development. This finding may be different for infants who remain inpatient until S2P, as those infants appeared to experience a more complicated clinical course than our sample. A previous NPC-QIC registry analysis demonstrated that infants who are not discharged after S1P have a slightly higher prevalence of any HM at S2P, but a lower prevalence of direct BF.[1] Future research is needed to determine whether there are differences in key HM/BF predictors for these infants.

Several variables related to clinical course were significant in the models but exhibited counterintuitive results (eg, need for reoperation after S1P associated with greater odds of any HM at S1P discharge; moderate/severe tricuspid regurgitation associated with greater odds of BF at S1P discharge). Further investigation revealed that these findings were likely driven by specific NPC-QIC sites. For example, two large sites reported a high prevalence of moderate/ severe tricuspid regurgitation (26% and 25%, compared to 17% average) while also achieving high direct BF prevalence at S1P discharge (48% and 24%, compared to 14% average). While individual sites could not be included in the models, these results reinforce our findings that institutional practices are important predictors of feeding outcomes for

infants with SV CHD.

Institutional site

Adjusting for infant race and insurance type, we found that the odds of any HM feeding, exclusive HM feeding, and direct BF varied widely among NPC-QIC sites, which builds on previous description of varied HM/BF prevalence among NPC-QIC sites.[1] Institutional culture and policy have been shown to impact HM/BF outcomes for both term and vulnerable infants.[71–73] Considering that feeding establishment for infants with SV CHD occurs under close healthcare team supervision, it is important to highlight that clinical practices predict HM/BF outcomes and that some practices are modifiable. Clinical practices that improve HM and BF outcomes for vulnerable neonates have been identified and include skin-to-skin contact with the lactating parent, oral care with colostrum, initial oral feeding at the breast, prenatal family education/lactation consultation, and staff lactation education.[39,48,74–76] Writing for the American Academy of Pediatrics, Parker et al.[48] outlined the need for a multidisciplinary approach to lactation support in the neonatal ICU, with consistent family/staff communication, physician buy-in, workflow integration, and data-driven feedback all factors that effectively support HM/BF. While this evidence may be transferable, research on clinical practices that support HM/BF for infants with critical CHD is currently sparse,[19,62,77–79] and few supportive practices have been tested clinically. Future work is needed to identify effective practices implemented by NPC-QIC institutions with above-average prevalence of HM feeding and direct BF.

A final clinical practice question involves fortification (ie, calorie goal ≥22 kcal/oz), as fortified feeding at S1P discharge was associated with 54% lower odds of any direct BF at the same time point. Due to risk for growth failure, fortification is ubiquitous for infants with SV CHD (eg, 92.8% of infants received fortification at S1P discharge in a recent NPC-QIC registry analysis).[1] Our findings align with qualitative accounts, in which parents of infants with critical CHD explained that routine fortification and rigid feeding protocols interfered with direct BF establishment.[19] Infants with SV CHD often receive

infant formula added to expressed HM bottle or tube feedings to increase calorie density. No HM-derived fortifiers are currently approved for this population in the US, although a 2022 randomized controlled trial[11] tested a potential new HM-based fortifier for infants with critical CHD. Alternative methods of fortification exist, but are not widely used in the US. For example, neonatal ICUs in Denmark – a country with high prevalence of preterm direct BF – routinely give concentrated, highly-fortified HM via syringe after BF (Ragnhild Måastrup, PhD, email communication, March 2021), and a 2023 study demonstrated improved growth for preterm infants fed hindmilk (ie, HM fractionated for high energy/fat content).[81] Future research should investigate fortification strategies that do not interfere with direct BF.

Limitations

While this large, multisite study using robust analysis addresses many shortcomings of single-site studies, we acknowledge limitations including those inherent to registry analysis such as potentially inaccurate or inconsistent data entry. These limitations may be mitigated by standardized data definitions and regular NPC-QIC data audits. However, feeding practices documented by healthcare providers may not represent infants' actual HM/BF status, particularly as parents of infants with critical CHD have reported going against feeding recommendations in order to protect direct BF.[19] Infants who were never discharged after S1P likely differed from those who were included in the analysis; therefore, results may not apply to all infants with SV CHD. This study was not intended to determine causation, and there could be relevant unmeasured variables including the lactating parent's feeding intention, previous HM/BF experience, education level, and country of origin. Furthermore, variables related to the infant's residential ZCTA provide an approximation of social and economic indicators but may not accurately represent an individual infant's situation. However, considering the lack of information about SDoH in feeding-related evidence for infants with CHD, inclusion of these variables is a step toward a broader understanding of the topic.

Conclusions

This study addresses the critical knowledge gap about HM feeding and direct BF for infants with SV CHD by identifying factors that are positively and negatively associated with these feeding practices at S1P discharge and at S2P, with preoperative feeding, demographics/ SDoH, feeding route, clinical course, and institutional site the strongest predictor domain. Based on the findings, we recommend that future research and practice focus on development and testing of family-centered, culturally-sensitive interventions to support HM and BF during the S1P preoperative time, as this first week of life appears to set the stage for the long-term nutrition of infants with SV CHD. Such interventions may be most effective if they offer cohesive support across the antenatal and perinatal times, include evidence-based strategies to address bias, seek to minimize disparities related to SDoH, and implement clinical practices common to high-performing NPC-QIC sites. Effective interventions are urgently needed to increase the current low rates of HM and direct BF for infants with SV CHD.

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Chapter 5: Human Milk Feeding and Direct Breastfeeding Improve Outcomes for Infants with Single Ventricle Congenital Heart Disease: Propensity Score Matched Analysis of the NPC-QIC Registry (Manuscript #3)

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Abstract

Background: Infants with single ventricle (SV) congenital heart disease (CHD) undergo three staged surgeries/interventions, with risk for morbidity and mortality. We estimated the effect of human milk (HM) and direct breastfeeding (BF) on outcomes including necrotizing enterocolitis (NEC), infection-related complications, length of stay (LOS), and mortality.

Methods: We analyzed the National Pediatric Cardiology Quality Improvement Collaborative registry (2016–2021), examining HM/BF groups during stage 1 (S1P) and stage 2 (S2P) palliations. We calculated propensity scores for feeding exposures, then fitted Poisson and logistic regression models to compare outcomes between propensity-matched cohorts.

Results: Participants included 2491 infants (68 sites). Estimates for all outcomes were better in HM/BF groups. Infants fed exclusive HM before S1P had lower odds of preoperative NEC (OR=0.37, 95% CI=0.17–0.84, p=0.017) and shorter S1P LOS (RR=0.87, 0.78–0.98, p=0.027). During the S1P hospitalization, infants with high HM had lower odds of postoperative NEC (OR=0.28, 0.15–0.50, p<0.001) and sepsis (0.29, 0.13–0.65, p=0.003), and shorter S1P LOS (RR=0.75, 0.66–0.86, p<0.001). At S2P, infants with any HM (0.82, 0.69–0.97, p=0.018) and any BF (0.71, 0.57–0.89, p=0.003) experienced shorter LOS.

Conclusions: Infants with SV CHD in high HM and BF groups experienced multiple significantly better outcomes. Given our findings of improved health, strategies to increase the rates of HM/BF in these patients should be implemented. Future research should replicate these findings with granular feeding data and in broader CHD populations, and should examine mechanisms (eg, HM components; microbiome) by which HM/BF benefits these infants.

Background

Children born with single ventricle congenital heart disease (SV CHD) are among the most vulnerable of pediatric populations. These infants undergo 3 staged palliative surgeries and/or catheter-based interventions and experience risk for morbidity (eg, necrotizing enterocolitis (NEC)),[1] developmental delay,[2] and family maladaptation[3,4] while incurring the highest hospital costs among United States (US) birth defects.[5] Mortality rates have been reduced by up to 38% over the past four decades;[6–8] yet, there remain opportunities to improve outcomes related to development and quality of life.[9]

Feeding for infants with SV CHD is one such developmental area in need of improvement. Human milk (HM) feeding and direct breastfeeding (BF) are agreed upon as the optimal nutrition of choice for hospitalized infants,[10,11] with a 2023 Science Advisory from the American Heart Association emphasizing that HM and BF are essential to developmental care for infants with critical CHD.[9] Yet, the SV CHD population has a prevalence of 7% exclusive HM and 9.4% any direct BF at approximately 5 months of age[12] – far below World Health Organization[10] and American Academy of Pediatrics[11] recommendations of exclusive HM feeding for the first 6 months of life, and below the US HealthyPeople 2030 objective of 42.4% exclusive BF through 6 months.[13] A recent study of lactating parents at 26 US cardiac centers described a lack of institutional and provider support of HM/BF for infants with critical CHD diagnoses including SV CHD.[14]

Inadequate lactation support could be reflective of limited evidence about HM/BF for this population.[9,15] Human milk and BF positively impact outcomes including NEC,[16] sepsis,[17] length of stay,[18] and mortality[19] for preterm infants and infants with surgical gastrointestinal anomalies. Little is known, however, about the benefits of HM and BF for infants with CHD. Emerging evidence suggests that exclusive HM feeding both before[20] and after[21] neonatal cardiac surgery may be protective against NEC — a disease with 19–26% mortality in CHD.[22] However, most studies of HM for infants with CHD

are limited by small sample size, heterogenous diagnoses, or risk for statistical bias.[15] Only one study[21] has examined HM and outcomes for infants specifically with SV physiology, focusing on the impact of an HM-based fortifier on weight gain. To our knowledge, there is no evidence focused on direct BF and outcomes for infants with CHD of any type. Thus, there is a critical gap in knowledge about HM/BF for infants with SV CHD.

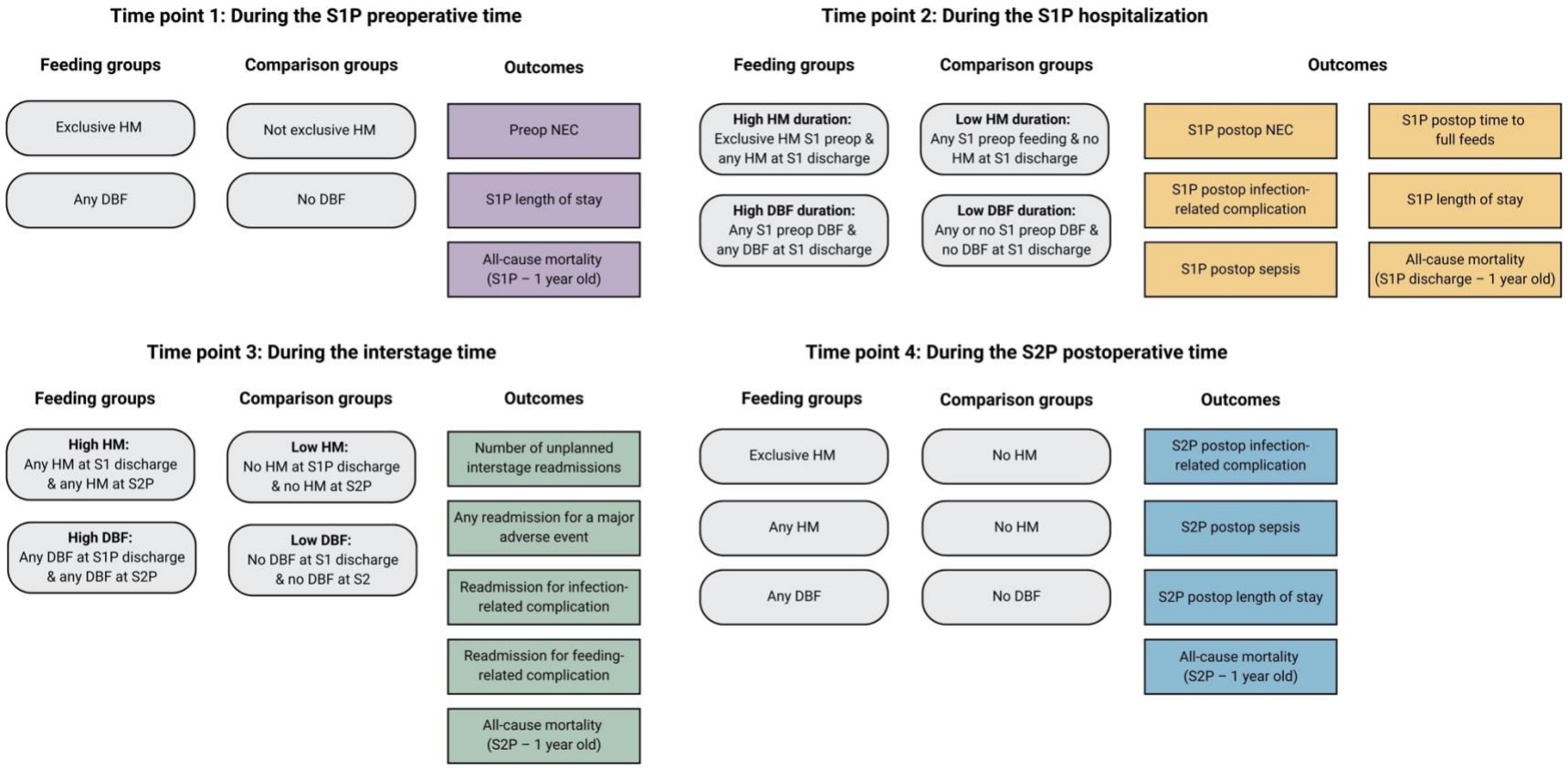
To address this gap in knowledge, we aimed to estimate the effect of HM feeding and direct BF on key outcomes in a large, multisite cohort of infants with SV CHD. We hypothesized that higher dose and/or duration of HM/BF would result in reduced prevalence of NEC, and that we would identify additional benefits related to infection-related complications (including sepsis), time to full feeding volume, hospital length of stay, unplanned hospital readmission, feeding-related hospital readmission, or all-cause mortality.

Methods

We conducted a propensity score matched cohort analysis of data from the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) registry, which includes infants with SV CHD from >60 US pediatric cardiology centers. Parental informed consent or waiver of consent for registry enrollment was obtained by each NPC-QIC site. For this study, infants with SV CHD who completed S1P were included. General exclusion criteria included family choice not to pursue treatment following birth and S1P admission >3 months of age. The University of Minnesota Institutional Review Board approved this study (STUDY00013371) and deemed it exempt from continuing review. All analyses were conducted using R (versions 4.2.1/4.2.2).[23]

Our definitions of HM feeding and direct BF, along with NPC-QIC registry feeding measures, have been previously described. Briefly, HM feeding included lactating parent/maternal human milk (MHM) or donor HM via any route, and direct BF was defined as HM directly from a lactating person. We assessed feeding exposures and outcomes at 4 time points (Figure 5.1). At time points 1 and 2, infants

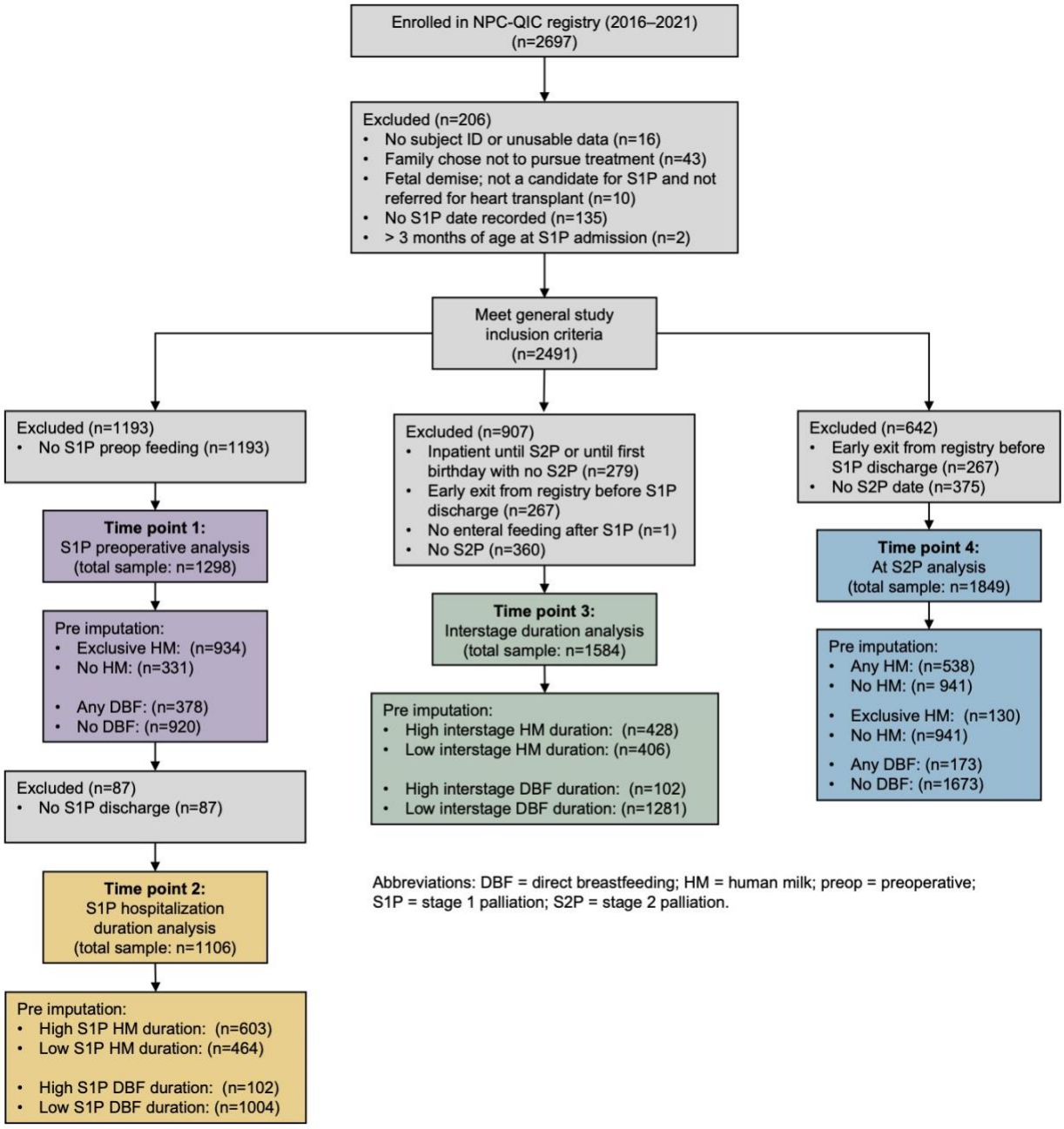
Figure 5.1. Feeding Groups, Outcomes, and Time Points Examined



Abbreviations: DBF = direct breastfeeding; HM = human milk; preop = preoperative; postop = postoperative; S1P = stage 1 palliation; S2P = stage 2 palliation.
Notes: To fulfill the propensity score assumption of positivity, time points 1 & 2 included only infants who were preoperatively fed.
Interstage refers to the time between S1P discharge and S2P.
Infection-related complications included pneumonia, sepsis, or sternal wound infection/dehiscence at all time points; admission requiring intravenous antibiotics for infection at the interstage time point.
Feeding-related complications included GERD, bloody stool, poor weight gain, or vomiting/diarrhea.

with no S1P preoperative feeding were excluded due to the propensity score assumption of positivity (ie, infants must have had a possibility of receiving the feeding exposure). At time point 3, which is based on S1P discharge data, infants who were never discharged between S1P and S2P were excluded. A flow diagram detailing reasons for inclusion and exclusion at each time point can be found in Figure 5.2.

Figure 5.2. Flow Diagram for Inclusion and Exclusion at all Study Time Points



At time point 2, we examined a high HM duration group including infants with exclusive HM preoperatively at S1P who were still receiving any HM at S1P discharge (see Figure 5.1). These infants were considered to have received HM throughout the course of the S1P hospitalization, in the absence of detailed longitudinal feeding data, and were compared to infants who received any type of preoperative feeding but who were no longer receiving HM at S1P discharge (ie, a low duration group). We examined similar high and low groups for S1P hospitalization duration of direct BF, and high and low HM/BF duration groups across the interstage period.

Outcomes (see Table 5.1) were selected based on literature from preterm, term, or other neonatal surgical populations demonstrating associations between HM and NEC,[16,17,24–26] infection,[27] sepsis,[17,28] time to full feeds,[29–31] feeding-related complications,[29,31] hospital length of stay,[29,30,32] and all-cause mortality.[17,19] Our approach to transformation of variables including prematurity, infant race, insurance type, weight-for-age (WAZ) and length-for-age (LAZ) z-scores, and social determinants of health (ie, rural-urban commuting area, median income of residential area, and social deprivation index (SDI))[33] has been previously described.[12]

Analysis

Across the sample, 3.1% of data were missing. We handled missing data via multiple imputation by chained equations (m=20) using the *mice* package[34] and including all potential covariates, exposure variables, and outcome variables.[34]

Table 5.1. Definitions of Outcomes and Time Points of Outcomes Assessment

Outcome	Definition	Time points
Necrotizing enterocolitis	Diagnosed per institution; treated medically or surgically	S1P preop S1P postop
S1P length of stay	Date of admission to date of initial discharge	S1P hospitalization
S2P postop length of stay	Date of S2P to date of initial discharge	S2P hospitalization
Infection-related complication	Diagnosed per institution; aggregate variable including pneumonia, sepsis, or sternal wound infection/dehiscence	S1P postop Interstage

	at all time points; admission requiring IV antibiotics for infection at the interstage time point	S2P postop
Sepsis	Diagnosed per institution	S1P postop S2P postop
Time to full feeds	Initial postop date on 100 kcal/kg/day enteral feeds	S1P postop
Interstage readmission for feeding-related complication	Diagnosed per institution; aggregate variable including GERD, bloody stool, poor weight gain, or vomiting/diarrhea	Interstage[a]
Number of unplanned interstage readmissions	Any readmission excluding planned pre-S2P cardiac catheterizations	Interstage[a]
Interstage readmission for major adverse event	Any readmission for aspiration, cardiac arrest, infection requiring intravenous antibiotics, cardiac shunt occlusion, life-threatening arrhythmia requiring cardioversion, seizure, or stroke	Interstage[a]
All-cause mortality	Death before first birthday; mortality was assessed following each time point of interest	S1P preop Post S1P discharge S2P postop

Abbreviations: GERD = gastroesophageal reflux disease; IV = intravenous; S1P = stage 1 palliation; S2P = stage 2 palliation; preop = preoperative time; postop = postoperative time.
[a]Interstage refers to the time between S1P discharge and S2P.

We conducted propensity score matched analyses using the *MatchThem* package[35] for imputed data to determine the average treatment effect among the treated (ATT). Propensity score matching supports causal inference with reduced bias and is particularly useful in HM/BF research, as true randomization is not possible. Propensity score models (ie, logistic regression models for the probability of being in the feeding group of interest) were created for each exposure/outcome combination (Table 5.2). As recommended by Brookhart et al.,[36] variables strongly related to the outcome were included in these models, while variables related to the exposure but not the outcome were excluded.

Propensity scores were calculated within each imputed data set, using nearest neighbor matching with a caliper ranging from 0.2–0.3 of the standard deviation of the logit of the propensity score. Matching ratios of up to 10:1 and matching with replacement were explored, with limits on the number of times a control could be reused. Covariate balance was assessed using the *cobalt* package[37] to obtain

Table 5.2. Details of Propensity Score Development for Feeding Exposure/Outcome Combinations at Time Points From the Stage 1 Palliation Preoperative Time To Stage 2 Palliation

	Sample size: Original cohort; Exposed/ Control	**Average n (%) of unmatched across imputations: Exposed/ Controls**	**Caliper/ k:1 ratio/ Max # of controls reused**	**Variables included in all propensity score models / Additional variables added to propensity score models for specific outcomes**	**Unbalanced variables added to outcome regression model**
S1P preoperative time					
Exclusive HM	N = 1265; 934/ 331			preterm, race, Hispanic/Latino/a ethnicity, insurance type, median income of ZCTA, SDI score of ZCTA, RUCA of ZCTA, age at S1P admission, WAZ at birth, primary & secondary cardiac diagnoses, other major anomalies, major genetic syndrome	
Preop NEC		1.95 (0.2)/ 11.3 (3.4)	0.2/ 4/10	/ N/A	N/A
S1P LOS		66.35 (7.1)/ 17.6 (5.3)	0.2/ 4/8	/ clinical site, comprehensive postnatal parental support	N/A
All-cause mortality		66.35 (7.1)/ 17.6 (5.3)	0.2/ 4/8	/ clinical site, comprehensive postnatal parental support	N/A
Any direct BF	N = 1298; 378/ 920			preterm, race, Hispanic/Latino/a ethnicity, insurance type, median income of ZCTA, SDI score of ZCTA, RUCA of ZCTA, age at S1P admission, WAZ at birth, primary & secondary cardiac diagnoses, other major anomalies, major genetic syndrome	
Preop NEC		0.25 (0.1)/	0.2/	/	N/A

		287.25 (31.2)	4/5	N/A	
S1P LOS		5.65 (1.5)/ 367.75 (40.0)	0.2/ 4/15	/ clinical site, comprehensive postnatal parental support, S1P preoperative instability	age at S1P admission, WAZ at birth
All-cause mortality		5.65 (1.5)/ 367.75 (40.0)	0.2/ 4/15	/ clinical site, comprehensive postnatal parental support, S1P preoperative instability	age at S1P admission, WAZ at birth
During the S1P hospitalization (preoperative – discharge)					
Exclusive HM preop & any HM at discharge vs. Any type of preop feeding & no HM at discharge	N = 1067; 603/ 464			preterm, race, Hispanic/Latino/a ethnicity, insurance type, median income of ZCTA, SDI score of ZCTA, RUCA of ZCTA, primary & secondary cardiac diagnoses, other major anomalies, major genetic syndrome, age at S1P admission, WAZ at birth, S1P preoperative instability, S1P surgical procedure, weaned inotropes and vasoactive meds within 5 days post-S1P, S1P CPB duration, S1P cross clamp duration, need for ECMO post-S1P, clinical site	
Postop NEC		6.95 (1.2)/ 77.5 (16.7)	0.2/ 4/20	/ N/A	SDI score of ZCTA
Infection-related postop complication (sepsis, pneumonia, wound infection)		7.3 (1.2)/ 85.4 (18.4)	0.2/ 4/20	/ delayed sternal closure post-S1P, intubation duration post-S1P	N/A
Postop sepsis		7.3 (1.2)/ 85.4 (18.4)	0.2/ 4/20	/ delayed sternal closure post-S1P, intubation duration post-S1P	N/A
Time to full feeds		7.3 (1.2)/ 85.4 (18.4)	0.2/ 4/20	/ delayed sternal closure post-S1P, intubation duration post-S1P	N/A
S1P LOS		6.8 (1.1)/ 87.75 (18.9)	0.2/ 4/15	/ intubation duration post-S1P, any major S1P	SDI score of ZCTA

				postop procedures, comprehensive postnatal parental support	
All-cause mortality		6.8 (1.1)/ 87.75 (18.9)	0.2/ 4/15	/ intubation duration post-S1P, any major S1P postop procedures, comprehensive postnatal parental support	SDI score of ZCTA
Any preop direct BF & any direct BF at discharge vs. Any type of preop feeding & no direct BF at S1P discharge	N = 1106; 102/ 1004			preterm, race, Hispanic/Latino/a ethnicity, insurance type, median income of ZCTA, SDI score of ZCTA, RUCA of ZCTA, primary & secondary cardiac diagnoses, other major anomalies, major genetic syndrome, age at S1P admission, WAZ at birth, S1P preoperative instability, S1P surgical procedure, weaned inotropes and vasoactive meds within 5 days post-S1P, S1P CPB duration, S1P cross clamp duration, need for ECMO post-S1P, clinical site	
Postop NEC		2.7 (2.7)/ 464.5 (46.3)	0.2/ 10/2	/ N/A	age at S1P admission, WAZ at birth
Infection-related postop complication (sepsis, pneumonia, wound infection)		2.95 (3.0)/ 730.6 (72.8)	0.3/ 10/10	/ delayed sternal closure post-S1P, intubation duration post-S1P	age at S1P admission, WAZ at birth, S1P CPB duration, S1P cross clamp duration, S1P surgical procedure, SDI score of ZCTA, median income of ZCTA
Postop sepsis		1.35 (1.3)/ 741.45 (73.9)	0.3/ 10/10	/ delayed sternal closure post-S1P, intubation duration post-S1P	age at S1P admission, WAZ at birth, S1P cross clamp duration, S1P surgical procedure, SDI score of ZCTA

Time to full feeds		1.35 (1.3)/ 741.45 (73.9)	0.3/ 10/10	/ delayed sternal closure post-S1P, intubation duration post-S1P	age at S1P admission, WAZ at birth, S1P CPB duration, S1P cross clamp duration, S1P surgical procedure, SDI score of ZCTA, median income of ZCTA
S1P LOS		1.35 (1.3)/ 741.45 (73.9)	0.3/ 10/10	/ intubation duration post-S1P, any major S1P postop procedures, comprehensive postnatal parental support	age at S1P admission, WAZ at birth, S1P cross clamp duration, S1P surgical procedure, SDI score of ZCTA
All-cause mortality		1.35 (1.3)/ 741.45 (73.9)	0.3/ 10/10	/ intubation duration post-S1P, any major S1P postop procedures, comprehensive postnatal parental support	age at S1P admission, WAZ at birth, S1P cross clamp duration, S1P surgical procedure, SDI score of ZCTA
During the interstage period (S1P discharge – S2P)					
Any HM at S1P discharge & any HM at S2P vs. No HM at S1P discharge & no HM at S2P	N = 836; 428/ 408			preterm, race, Hispanic/Latinx ethnicity, insurance type, median income of ZCTA, SDI score of ZCTA, RUCA of ZCTA, primary & secondary cardiac diagnoses, other major anomalies, major genetic syndrome, S1P hospital LOS, G-tube at S1P discharge, S1P discharge WAZ, S1P discharge LAZ, clinical site	
# of unplanned interstage readmissions Interstage readmission for adverse event Infection-related interstage readmission Feeding-related interstage readmission All-cause mortality		0 (0.0)/ 96.4 (23.6)	0.2/ 8/20	N/A	S1P discharge LAZ, S1P hospital LOS

Any direct BF at S1P discharge & any direct BF at S2P vs. No direct BF at S1P discharge & no direct BF at S2P	N = 1383; 102/ 1281			preterm, race, Hispanic/Latinx ethnicity, insurance type, median income of ZCTA, SDI score of ZCTA, RUCA of ZCTA, primary & secondary cardiac diagnoses, other major anomalies, major genetic syndrome, S1P hospital LOS, G-tube at S1P discharge, S1P discharge WAZ, S1P discharge LAZ, clinical site	
# of unplanned interstage readmissions Interstage readmission for adverse event Infection-related interstage readmission Feeding-related interstage readmission All-cause mortality		2.9 (2.8)/ 989.35 (70.6)	0.2/ 10/10		S1P discharge WAZ, SDI score of ZCTA, S1P hospital LOS
At S2P					
Any HM vs. No HM	N = 1847; 785/ 1062			preterm, race, Hispanic/Latinx ethnicity, insurance type, median income of ZCTA, SDI score of ZCTA, RUCA of ZCTA, primary & secondary cardiac diagnoses, other major anomalies, major genetic syndrome, S1P hospital LOS, G-tube at S2P, WAZ at S2P, LAZ at S2P, age at S2P, aortic regurgitation at S2P, discharged between S1P and S2P, clinical site	
S2P postop LOS; Infection-related S2P postop complication S2P postop sepsis All-cause mortality		2.85 (0.0)/ 243.3 (22.9)	0.2/ 4/10	/ N/A	N/A

Exclusive HM vs. No HM	N = 1077; 130/ 947			preterm, race, Hispanic/Latinx ethnicity, insurance type, median income of ZCTA, SDI score of ZCTA, RUCA of ZCTA, primary & secondary cardiac diagnoses, other major anomalies, major genetic syndrome, S1P hospital LOS, G-tube at S2P, WAZ at S2P, LAZ at S2P, age at S2P, aortic regurgitation at S2P, discharged between S1P and S2P, clinical site	
S2P postop LOS Infection-related S2P postop complication S2P postop sepsis All-cause mortality		1.35 (1.0)/ 533.8 (56.4)	0.2/ 10/2	/ N/A	N/A
Any direct BF vs. No direct BF	N = 1847; 173/ 1674			preterm, race, Hispanic/Latinx ethnicity, insurance type, median income of ZCTA, SDI score of ZCTA, RUCA of ZCTA, primary & secondary cardiac diagnoses, other major anomalies, major genetic syndrome, S1P hospital LOS, G-tube at S2P, WAZ at S2P, LAZ at S2P, age at S2P, aortic regurgitation at S2P, discharged between S1P and S2P, clinical site	
S2P postop LOS Infection-related S2P postop complication S2P postop sepsis All-cause mortality		4.1 (2.4)/ 1009.2 (60.3)	0.2/ 10/2	/ N/A	N/A

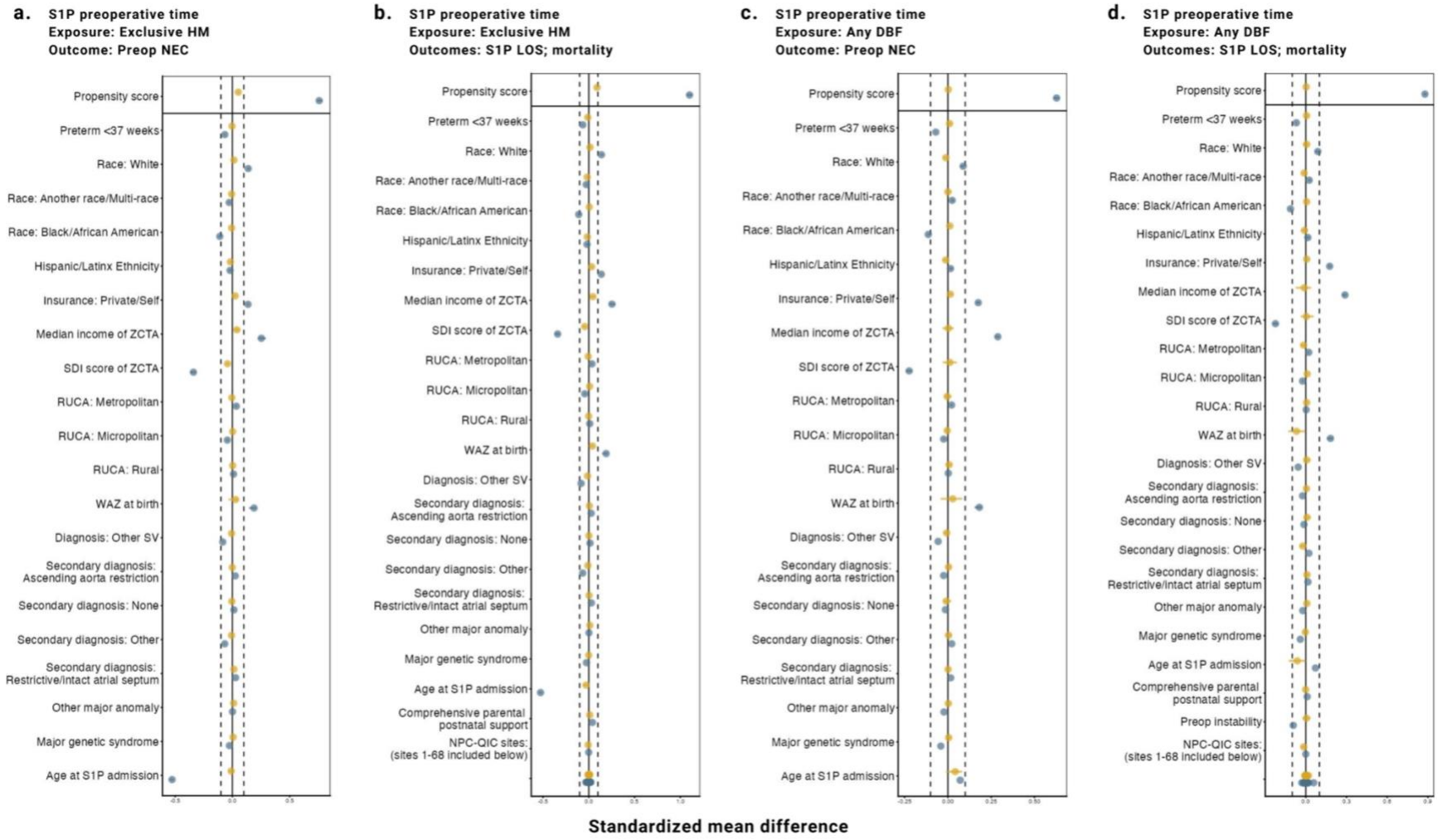
Abbreviations: BF = breastfeeding; CPB = cardiopulmonary bypass; ECMO = extracorporeal membrane oxygenation; G-tube = gastrostomy; HM = human milk; LAZ = length-for-age z-score; LOS = length of stay; RUCA = rural-urban commuting area; S1P = stage 1 palliation; S2P = stage 2 palliation; SDI = social deprivation index; WAZ = weight-for-age z-score; ZCTA = zip code tabulation area.

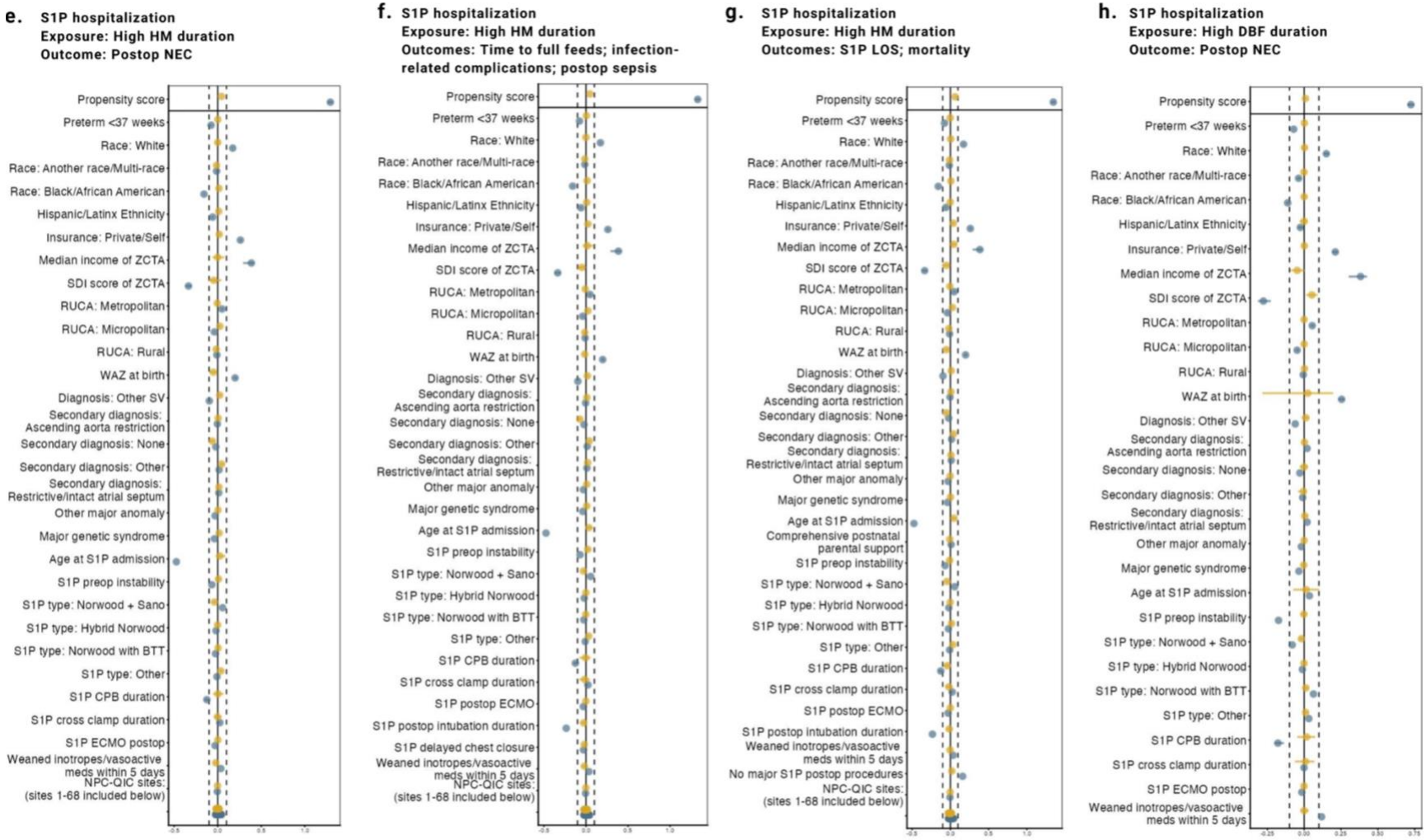
absolute standardized mean differences (SMD; ie, the largest SMD for each covariate across imputations[35]), with an SMD <0.10 considered to be acceptably balanced. We considered interaction and polynomial terms to aid in covariate balance, and those covariates that could not be balanced were included in the final outcome regression models. Further details of propensity score models are found in Table 5.2, and covariate balance visualized in Figures 5.3 and 5.4.

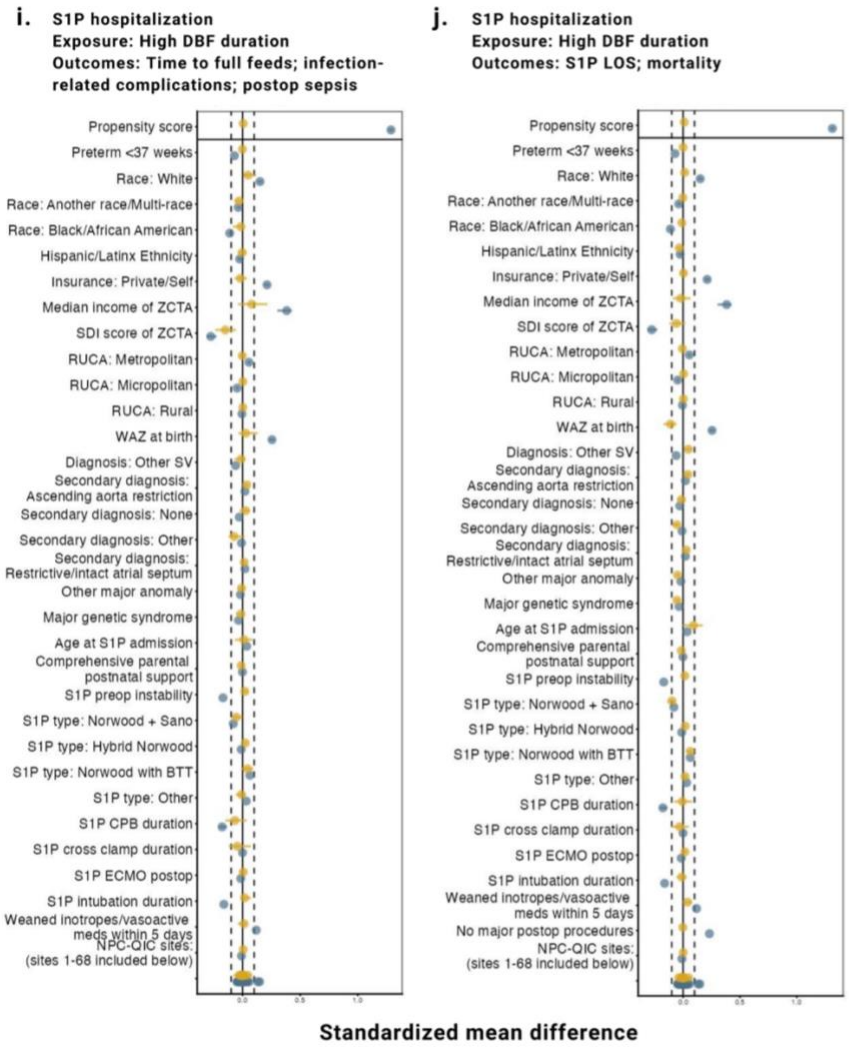
We fitted Poisson or logistic regression models to compare outcomes between propensity matched cohorts using the "svlglm" function from the *survey* package[38] for robust standard error calculation,[35] with Rubin's[39] rules used to obtain pooled odds ratios (OR) or rate ratios (RR) and 95% confidence intervals (CI). Poisson regression was used to model the outcomes of hospital length of stay, time to full feeds, and the number of unplanned interstage readmissions, with models fitted for these outcomes using a Gaussian distribution for comparison. Logistic regression models were fitted for the remaining binary outcomes. For rare binary outcomes resulting in issues with separation (eg, 0% outcome prevalence in one feeding group), logistic regression models were refitted with mean bias-reducing score adjustment[40,41] using the "brglmFit" function in the *brglm2* package.[42] Sensitivity analysis included inverse probability weighting using the propensity score to calculate the ATT on the same imputed data.

Covariate selection for the analyses examining HM or BF during the S1P hospitalization (Figure 5.1, time point 2) was challenging, as we were unable to determine dates of, for example, major postoperative procedures or complications. Therefore, we were liberal in including potentially important covariates in propensity score models for the main analyses and also conducted sensitivity analyses using propensity score models with more limited, baseline covariates.

Figure 5.3. Visualization of Standardized Mean Differences Indicating Covariate Balance in the Original Cohort and After Propensity Score Matching for Exposures and Outcomes Examined During the Stage 1 Palliation Hospitalization




e. S1P hospitalization
Exposure: High HM duration
Outcome: Postop NEC
f. S1P hospitalization
Exposure: High HM duration
Outcomes: Time to full feeds; infection-related complications; postop sepsis
g. S1P hospitalization
Exposure: High HM duration
Outcomes: S1P LOS; mortality
h. S1P hospitalization
Exposure: High DBF duration
Outcome: Postop NEC
Propensity score
Preterm <37 weeks
Race: White
Race: Another race/Multi-race
Race: Black/African American
Hispanic/Latinx Ethnicity
Insurance: Private/Self
Median income of ZCTA
SDI score of ZCTA
RUCA: Metropolitan
RUCA: Micropolitan
RUCA: Rural
WAZ at birth
Diagnosis: Other SV
Secondary diagnosis: Ascending aorta restriction
Secondary diagnosis: None
Secondary diagnosis: Other
Secondary diagnosis: Restrictive/intact atrial septum
Other major anomaly
Major genetic syndrome
Age at S1P admission
Comprehensive postnatal parental support
S1P preop instability
S1P type: Norwood + Sano
S1P type: Hybrid Norwood
S1P type: Norwood with BTT
S1P type: Other
S1P CPB duration
S1P cross clamp duration
S1P postop ECMO
S1P postop intubation duration
S1P delayed chest closure
Weaned inotropes/vasoactive meds within 5 days
No major S1P postop procedures
NPC-QIC sites: (sites 1-68 included below)
Standardized mean difference



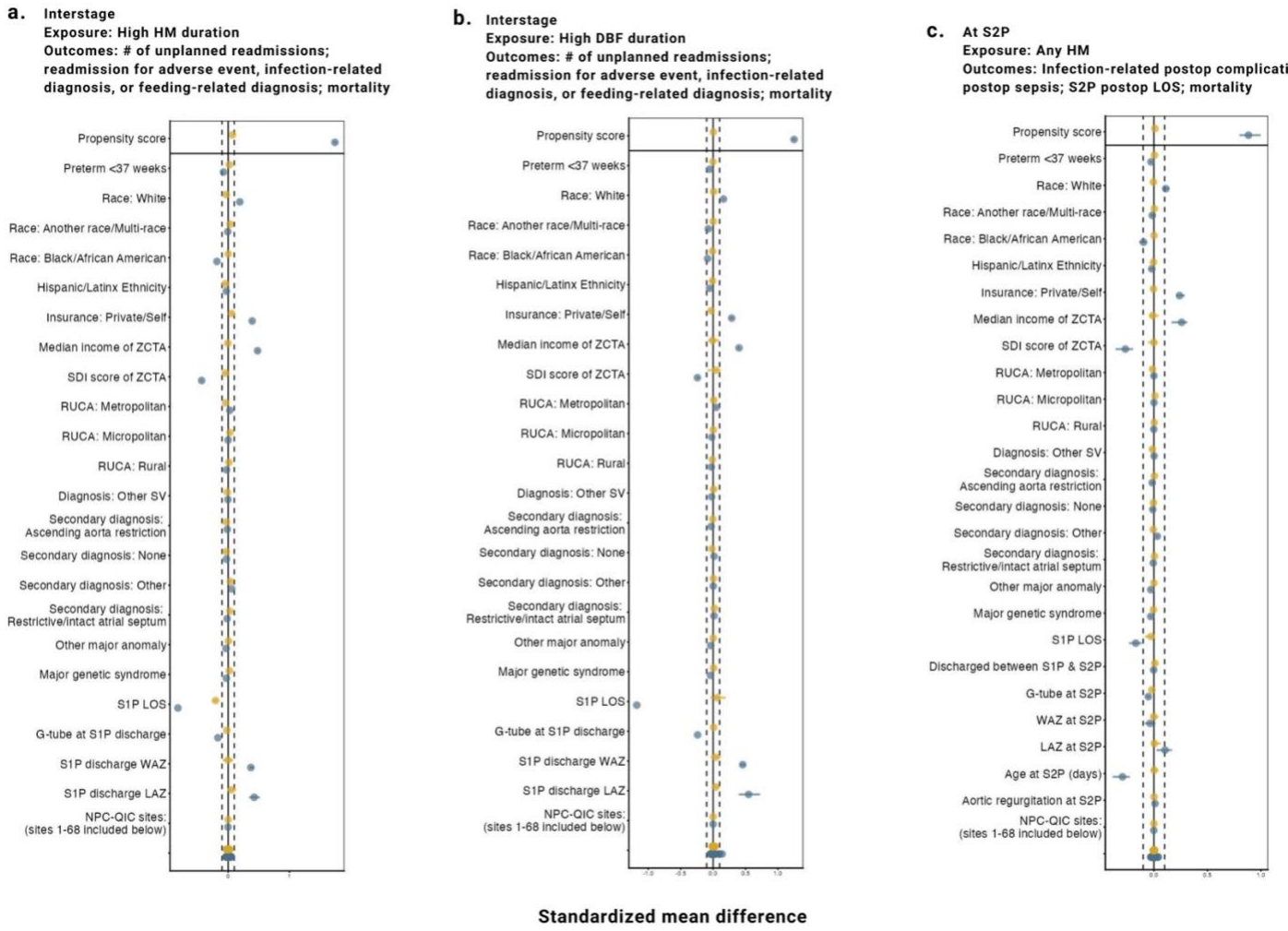
Abbreviations: BTT = Blalock–Thomas–Taussig shunt; CPB = cardiopulmonary bypass; DBF = direct breastfeeding; ECMO = extracorporeal membrane oxygenation; HM = human milk; NPC-QIC = National Pediatric Cardiology Quality Improvement Collaborative; RUCA = rural-urban commuting area; S1P = stage 1 palliation; SDI = social deprivation index; SV = single ventricle; WAZ = weight-for-age z-score; ZCTA = zip code tabulation area

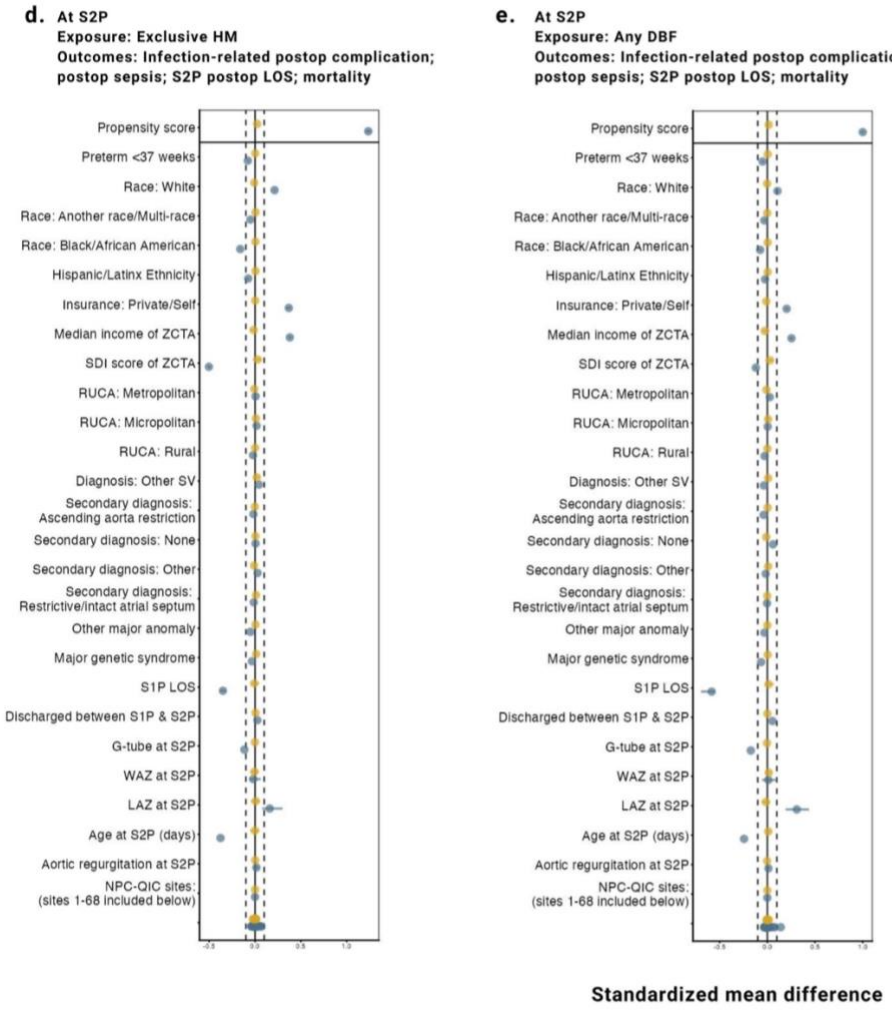
Notes: Dotted lines are at -0.10 and 0.10. Points within the dotted lines indicate an absolute standardized mean difference <0.10.

The matched sample indicates the largest absolute standardized mean difference after matching across all the imputed data sets.

Covariates listed are the variables included in the logistic regression model to create the propensity score for the indicated exposure/outcome combination.

Figure 5.4. Visualization of Standardized Mean Differences Indicating Covariate Balance in the Original Cohort and After Propensity Score Matching for Exposures and Outcomes Examined During the Interstage Period and at Stage 2 Palliation





Abbreviations: DBF = direct breastfeeding; G-tube = gastrostomy tube; HM = human milk feeding; LAZ = length-for-age z-score; NPC-QIC = National Pediatric Cardiology Quality Improvement Collaborative; RUCA = rural-urban commuting area; S1P = stage 1 palliation; S2P = stage 2 palliation; SDI = social deprivation index; SV = single ventricle; WAZ = weight-for-age z-score; ZCTA = zip code tabulation area.

Notes: Dotted lines are at -0.10 and 0.10. Points within the dotted lines indicate an absolute standardized mean difference <0.10.

The matched sample indicates the largest absolute standardized mean difference after matching across all the imputed data sets.

Covariates listed are the variables included in the logistic regression model to create the propensity score for the indicated exposure/outcome combination.

Results

Of 2697 infants in the NPC-QIC registry, 2491 from 68 sites met general study inclusion criteria. Of note, all infants diagnosed with S1P preoperative NEC completed S1P and were included in the study. Key sample characteristics and sample-wide outcomes can be found in Table 5.3.

Table 5.3. Characteristics and Outcomes of Interest Among the Full National Pediatric Cardiology Quality Improvement Project Registry Sample (N = 2491)

Sample characteristics: mean (SD) or n (%)		Outcomes of interest: mean (SD) or n (%)	
Sex		S1P preop NEC	
Female	988 (39.7)	Yes	58 (2.3)
Male	1501 (60.3)	No	2433 (97.7)
Ambiguous or Unknown	2 (0.1)	S1P postop NEC	
Race		Yes	324 (13.0)
Another Race/Multi-Race	297 (12.3)	No	2167 (87.0)
Black/African American	397 (16.4)	S1P postop infection-related complication[a]	
White	1721 (71.3)	Yes	386 (15.5)
(Unknown)	76	No	2105 (84.5)
Hispanic or Latino/a Ethnicity		S1P postop sepsis	
Yes	390 (16.4)	Yes	98 (5.1)
No	1987 (83.6)	No	1842 (94.9)
(Unknown)	114	(Unknown)	551
Insurance type		S1P postop time to full feeds (d)	16 (17)
Government	1302 (54.6)	(Unknown)	254
Private/Self	1084 (45.4)	S1P length of stay (d)	48 (32)
(Unknown)	105	(Unknown)	550
Median income of ZCTA	65,667 (23,849)	# of unplanned interstage readmits	1.92 (1.27)
(Unknown)	69	(Unknown)	1527
SDI score of ZCTA	51 (28)	Interstage admit for major adverse event[b]	
(Unknown)	63	Yes	67 (7.0)
Rural-urban commuting area		No	897 (93.0)
Metropolitan	1971 (81.1)	(Unknown)	1527
Micropolitan	254 (10.5)	Interstage admit for infection-related complication[a]	
Rural	204 (8.4)	Yes	136 (14.1)
(Unknown)	62	No	828 (85.9)
Preterm (<37 weeks)		(Unknown)	1527
Yes	307 (12.4)	Interstage admit for feeding-related complication[c]	
No	2161 (87.6)	Yes	357 (37.0)
(Unknown)	23	No	607 (63.0)
WAZ at birth	-0.18 (1.10)	(Unknown)	1527
(Unknown)	73		
Primary cardiac diagnosis		S2P postop infection-related complication[a]	
HLHS	1757 (70.5)	Yes	107 (5.8)
Other SV	734 (29.5)	No	1739 (94.2)

Secondary cardiac diagnosis	
Ascending aorta restriction	220 (8.8)
Restrictive/intact atrial septum	1378 (55.3)
Other	640 (25.7)
None	253 (10.2)
Other major anomaly	
Yes	190 (7.6)
No	2301 (92.4)
Major genetic syndrome	
Yes	314 (12.6)
No	2177 (87.4)
Age at S1P admission	1.13 (4.87)
Comprehensive parental postnatal support	
Yes	2360 (94.7)
No	131 (5.3)
S1P preoperative enteral feeding	
Yes	1440 (57.8)
No	1051 (42.2)
Discharged after S1	
Yes	2205 (89.5)
No	259 (10.5)
(Unknown)	27
(Unknown)	645
S2P postop sepsis	
Yes	62 (3.4)
No	1779 (96.6)
(Unknown)	650
S2P postop LOS	19 (24)
(Unknown)	758
All-cause mortality[d]	
Yes	357 (14.3)
No	2134 (85.7)

Abbreviations: d = days; HLHS = hypoplastic left heart syndrome; LOS = length of stay; NA = not applicable; NEC = necrotizing enterocolitis, postop = postoperative; preop = preoperative; S1P = stage 1 palliation; S2P = stage 2 palliation, SV = single ventricle; ZCTA = zip code tabulation area.

[a]Includes pneumonia, sepsis, wound infection/dehiscence, and (in interstage) infection requiring intravenous antibiotics.

[b]Includes aspiration, cardiac arrest, infection requiring intravenous antibiotics, cardiac shunt occlusion, life-threatening arrhythmia requiring cardioversion, seizure, and stroke.

[c]Includes gastroesophageal reflux disease, bloody stool, poor weight gain, and vomiting/diarrhea

[d]Between stage 1 palliation and 1 year of age.

Propensity score matched analyses

S1P hospitalization. The estimates for all S1P hospitalization outcomes were better in the high HM and BF groups, although not all reached statistical significance (see Tables 5.4 and 5.5). Infants with SV CHD who were preoperatively fed exclusive HM had 63% lower odds of preoperative NEC (OR=0.37, 95% CI=0.17–0.84, p=0.017) and a 13% reduction in mean S1P length of stay (RR=0.87, 0.78–0.98, p=0.027).

Infants with high HM feeding duration across the S1P hospitalization had 72% lower odds of postoperative NEC (0.28, 0.15–0.50, p<0.001), 52% lower odds of an infection-related postoperative complication (0.48, 0.25–0.91, p=0.025), 71% lower odds of postoperative sepsis (0.29, 0.13–0.65, p=0.003), and a 25% reduction in S1P length of stay (RR=0.75, 0.66–0.86, p<0.001).

Infants with high direct BF duration across the S1P hospitalization had 100% lower odds of postoperative sepsis in the main analysis, with a similar result in the bias-corrected sensitivity analysis

(OR=0.07, 0.02–0.22, p<0.001). In the unmatched cohort, this finding corresponded to 0% vs. 6.6% prevalence of S1P postoperative sepsis in the high vs. low BF duration groups. Infants with high BF duration also had a 23% reduction in S1P length of stay (0.77, 0.66–0.90, p=0.001).

Interstage and S2P hospitalization. The results of the propensity score matched analyses for the interstage and S2P hospitalization time points are in Tables 5.6 and 5.7. Again, the estimates for all outcomes were slightly-to-substantially better in the high HM and BF groups. Infants with high interstage BF duration had 100% lower odds of mortality between S2P and 1 year old in the main analysis, corresponding to 0% vs. 3.3% prevalence in high vs. low BF groups in the unmatched sample and 77% reduced odds in the bias-corrected analysis (0.23, 0.09–0.58, p=0.002).

Table 5.4. Average Treatment Effect Among the Treated of Exclusive Human Milk Feeding and Any Direct Breastfeeding During the Stage 1 Palliation Preoperative Time for Key Outcomes in Propensity Score Matched Cohorts

	OR or RR	95% CI	p value
Exclusive HM (*n*=934) vs. Not exclusive HM (*n*=331)			
Outcome			
Preop NEC	0.37[a]	(0.17–0.84)	**0.017**
S1P hospital LOS	0.87[b]	(0.78–0.98)	**0.027**
All-cause mortality[c]	0.70[a]	(0.46–1.07)	0.099
Any DBF (n=378) vs. No DBF (n=920)			
Outcome			
Preop NEC	0.73[a]	(0.25–2.12)	0.566
S1P hospital LOS	0.94[b]	(0.83–1.07)	0.361
All-cause mortality[c]	0.73[a]	(0.44–1.21)	0.227

Abbreviations: CI = confidence interval; DBF = direct breastfeeding; HM = human milk; LOS = length of stay; NEC = necrotizing enterocolitis; OR = odds ratio; preop = preoperative; RR = rate ratio.
[a]Analysis included logistic regression; estimate presented as odds ratio.
[b]Analysis included Poisson regression; estimate presented as rate ratio.
[c]Between stage 1 palliation and 1 year of age.

Table 5.5. Average Treatment Effect Among the Treated of High Human Milk Feeding or Direct Breastfeeding Duration in the Stage 1 Palliation Hospitalization for Key Outcomes in Propensity Score Matched Cohorts

	OR or RR	95% CI	p value
High HM duration: Exclusive preop HM + any HM at discharge (n=603) vs. Low HM duration: Any type of preop feeding but no HM at discharge (n=464)			
Outcome			
Postop NEC	0.28[a]	(0.15–0.50)	**<0.001**
Infection-related postop complication[c]	0.48[a]	(0.25–0.91)	**0.025**
Postop sepsis	0.29[a]	(0.13–0.65)	**0.003**
Time to full feeds	0.95[b]	(0.82–1.10)	0.492
S1P hospital LOS	0.75[b]	(0.66–0.86)	**<0.001**
All-cause mortality[d]	0.54[a]	(0.20–1.46)	0.226
High DBF duration: Any preop DBF + any DBF at discharge (n=102) vs. Low DBF duration: Any type of preop feeding but no DBF at discharge (n=1004)			
Outcome			
Postop NEC	0.67[a]	(0.29–1.56)	0.355
Infection-related postop complication[c]	0.66[a]	(0.20–2.21)	0.501
Postop sepsis	0.00[a]	NC[e]	**<0.001**
Time to full feeds	0.89[b]	(0.71–1.12)	0.317
S1P hospital LOS	0.77[b]	(0.66–0.90)	**0.001**
All-cause mortality[d]	0.25[a]	(0.03–2.29)	0.218

Abbreviations: CI = confidence interval; DBF = direct breastfeeding; HM = human milk; LOS = length of stay; NEC = necrotizing enterocolitis; OR = odds ratio; postop = postoperative; preop = preoperative; RR = rate ratio; S1P = stage 1 palliation.
[a]Analysis included logistic regression; estimate presented as odds ratio.
[b]Analysis included Poisson regression; estimate presented as rate ratio.
[c]Includes postoperative pneumonia, sepsis, and wound infection.
[d]Between stage 1 palliation and 1 year of age.
[e]Due to rare occurrence of the outcome, confidence intervals were not computable.

Table 5.6. Average Treatment Effect Among the Treated of High Interstage Human Milk Feeding or Direct Breastfeeding Duration (Stage 1 Palliation Discharge to Stage 2 Palliation) for Key Outcomes in Propensity Score Matched Cohorts

	OR or RR	95% CI	p value
High interstage HM duration: Any HM at S1P discharge + any HM at S2P (n=428) vs. Low interstage HM duration: No HM at S1P discharge + no HM at S2P (n=408)			
Outcome			
# of unplanned interstage readmissions	0.97[a]	(0.72–1.30)	0.835
Any interstage readmission for adverse events[c]	0.89[b]	(0.52–1.54)	0.684
Infection-related interstage readmission[d]	0.86[b]	(0.30–2.45)	0.684
Feeding-related interstage readmission[e]	0.66[b]	(0.30–1.47)	0.310
All-cause mortality[f]	0.31[b]	(0.04–2.63)	0.284

High interstage DBF duration: Any DBF at S1P discharge + any DBF at S2P (n=102) vs. Low interstage DBF duration: No DBF at S1P discharge + no DBF at S2P (n=1281)			
Outcome			
# of unplanned interstage readmissions	0.89[a]	(0.61–1.30)	0.531
Any interstage readmission for adverse events[c]	0.97[b]	(0.54–1.74)	0.911
Infection-related interstage readmission[d]	0.97[b]	(0.32–2.98)	0.959
Feeding-related interstage readmission[e]	0.46[b]	(0.20–1.06)	0.069
All-cause mortality[f]	0.00[b]	NC[g]	**<0.001**

Abbreviations: CI = confidence interval; DBF = direct breastfeeding; HM = human milk; NC = not computable; OR = odds ratio; RR = rate ratio; S1P = stage 1 palliation; S2P = stage 2 palliation.
[a]Analysis included Poisson regression; estimate presented as rate ratio.
[b]Analysis included logistic regression; estimate presented as odds ratio.
[c]Includes aspiration, cardiac arrest, infection requiring intravenous antibiotics, cardiac shunt occlusion, life-threatening arrhythmia requiring cardioversion, seizure, and stroke.
[d]Includes pneumonia, sepsis, wound infection/dehiscence, and infection requiring intravenous antibiotics.
[e]Includes gastroesophageal reflux disease, bloody stool, poor weight gain, and vomiting/diarrhea.
[f]Between stage 2 palliation and 1 year of age.
[g]Due to rare occurrence of the outcome, confidence intervals were not computable.

Table 5.7. Average Treatment Effect Among the Treated of Human Milk Feeding and Direct Breastfeeding at Stage 2 Palliation for Key Outcomes in Propensity Score Matched Cohorts

	OR or RR	**95% CI**	**p value**
Any HM at S2P (n=785) vs. No HM at S2P (n=1062)			
Outcome			
Infection-related S2P postop complication[c]	0.94[a]	(0.53–1.68)	0.838
S2P postop sepsis	0.61[a]	(0.28–1.30)	0.196
S2P postop hospital LOS	0.82[b]	(0.69–0.97)	**0.018**
All-cause mortality[d]	0.85[a]	(0.41–1.76)	0.661
Exclusive HM at S2P (n=130) vs. No HM at S2P (n=947)			
Outcome			
Infection-related S2P postop complication[c]	0.56[a]	(0.16–1.92)	0.353
S2P postop sepsis	0.49[a]	(0.12–1.98)	0.315
S2P postop hospital LOS	0.75[b]	(0.57–0.99)	**0.040**
All-cause mortality[d]	0.49[a]	(0.18–1.35)	0.166
Any DBF at S2P (n=173) vs. No DBF at S2P (n=1674)			
Outcome			
Infection-related S2P postop complication[c]	0.39[a]	(0.11–1.34)	0.136
S2P postop sepsis	0.87[a]	(0.18–4.12)	0.861
S2P hospital LOS	0.71[b]	(0.57–0.89)	**0.003**
All-cause mortality[d]	0.24[a]	(0.03–1.88)	0.174

Abbreviations: CI = confidence interval; DBF = direct breastfeeding; HM = human milk; LOS = length of stay; NEC = necrotizing enterocolitis; postop = postoperative; OR = odds ratio; RR = rate ratio; S2P = stage 2 palliation
[a]Analysis included logistic regression; estimate presented as odds ratio
[b]Analysis included Poisson regression; estimate presented as rate ratio
[c]Includes postoperative pneumonia, sepsis, and wound infection
[d]Between stage 2 palliation and 1 year of age

At S2P, all HM/BF groups had a significant reduction in postoperative hospital length of stay with mean reductions of 18% (0.82, 0.69–0.97, p=0.018) for any HM; 25% (0.75, 0.57–0.99, p=0.040) for exclusive HM, and 29% (0.71, 0.57–0.89, p=0.003) for any BF.

Sensitivity analyses

The results of sensitivity analyses using inverse probability weighting; limited baseline covariates for S1P hospitalization propensity score models; and Gaussian distribution for hospital length of stay, time to full feeds, and interstage readmissions supported the main conclusions of the above analyses, with estimates that were similar in direction and magnitude (see Supplementary Material in Appendix D).

Discussion

This study addresses a critical gap in knowledge as the first large, multisite analysis of the relationship between HM or direct BF and several key outcomes for infants with SV CHD. In our propensity score matched cohorts, all outcome estimates at four time points during the first year of life were better in HM/BF groups, with many results reaching statistical significance and substantial clinical significance across the board. We will focus our discussion on results relating to NEC, sepsis and infection, length of stay, and mortality.

Necrotizing enterocolitis

We found that infants with higher exposure to HM feeding had lower odds of S1P preoperative and postoperative NEC. These findings are consistent with two decades of research in preterm populations, and are important in light of a 2022 review by Burge et al.[43] outlining potential differences between NEC in preterm infants and the cardiac NEC experienced by infants with CHD. Burge and colleagues suggested that cardiac NEC is, in part, a function of impaired gut perfusion, with resulting hypoperfusion and mesenteric ischemia contributing to an endothelial inflammatory response with associated gut permeability and pathogenic translocation. Dysbiosis of the gut microbiome related to high

systemic inflammation,[44] prophylactic antibiotics, and delayed enteral feeding are known to play a role in NEC and intestinal injury in neonates.[43]

Despite potential differences in etiology between preterm and cardiac NEC, our findings suggest that the protective benefits of HM demonstrated for preterm infants extrapolate to the SV CHD population. Four recent systematic reviews and meta-analyses[16,16,24,26] demonstrate convincing reductions in preterm NEC due to provision of HM and/or avoidance of infant formula (eg, 68% reduced risk;[25] 4% lower incidence[16]). Few previous studies, however, have examined the relationship between HM and NEC in infants with CHD.[20,21,45] Our results align with Cognata et al.'s[20] well-designed retrospective cohort study which reported 83% lower odds of preoperative NEC for exclusive HM-fed infants with critical CHD.

In another study conducted at the same institution as in Cognata et al., with the same population,[20] Kataria-Hale et al.[45] found no difference in postoperative NEC related to exclusive preoperative HM. The authors hypothesized that postoperative feeding practices at the time of NEC development may have been more influential. Our findings lend support to this hypothesis, as infants with high HM feeding during the S1P hospitalization had 72% lower odds of postoperative NEC. This result is particularly intriguing, as the literature regarding critical CHD has often focused on preoperative NEC due to controversy about the safety of preoperative enteral feeding. However, the prevalence of postoperative NEC, as diagnosed per institution, was higher in our sample (ie, 13.0% postoperatively vs. 2.3% preoperatively), emphasizing the need to reduce NEC throughout the entire S1P hospitalization. We also recommend further examination of the type, timing, and delivery mode of milk fortification as standard postoperative protocol. While Blanco et al.'s[21] 2022 randomized controlled trial (RCT) testing an HM-based fortifier suggests that an exclusive HM diet may reduce the incidence of postoperative NEC for infants with SV CHD, this fortifier is not yet available in the US and the study was not powered for the NEC outcome. Exposure to bovine-milk-based fortifier/formula, which has been shown to increase the risk of NEC,[46] is the current standard

of care. Future research is needed to identify ways to increase the dose and duration of postoperative HM while supporting growth and development, with exclusive HM feeding a potentially critical intervention to reduce NEC-related morbidity and mortality for infants with SV CHD.

Potential mechanisms. In recent years, there has been increased focus on the cellular, molecular, and nutritional composition of HM and on the relationship between HM and the infant gut microbiome-immune axis. Research has elucidated mechanisms influencing the development of NEC in preterm infants, with HM components such as HM oligosaccharides,[47–50] exosomes,[51,52] fatty acids and lipids,[53] lactoferrin,[54] immunoglobulins,[54,55] and many other bioactive factors[56] offering tailored protection against NEC and other hospital-associated diseases. Emerging evidence reveals that HM from the infant's own lactating parent (ie, MHM) is associated with epigenetic variation in DNA methylation,[57,58] which may provide protection against oxidative stress that could contribute to NEC. These HM components are closely related to healthy development of the infant gut microbiome.[59] Studies have characterized the gastrointestinal microbiome[60] of preterm populations, revealing frequent dysbiosis driven by exposure to infant formula, antibiotics, and delivery mode (ie, cesarean section) that could contribute to NEC.[61] Interestingly, two 2022 RCTs[62,63] examining infant fortifiers highlight the crucial role of MHM in positively shaping the preterm gastrointestinal microbiome, with Kumbhare et al.[62] identifying volume of MHM as the strongest predictor of the preterm infant's gut microbiota.

Knowledge about the gut microbiome of infants with CHD is only beginning to emerge,[64–69] and there has been no investigation into HM composition in the context of CHD. A 2022 study by Huang et al.[64] provides the first comprehensive evidence on the gut microbiome of neonates with critical CHD, reporting dysbiosis characterized by increased pathogens (eg, *Enterococcaceae*, *Enterobacteriaceae*) and decreased beneficial organisms (eg, *Bifidobacterium*, *Lactobacillus*) – a profile that shares similarities with the gut microbiome of very-low-birth-weight infants[60] – with consequent inflammatory and immune imbalances potentially contributing to poor clinical outcomes, including NEC. Huang and colleagues note

the key role of HM/BF (eg, human milk oligosaccharides) in establishing normal gut *Bifidobacterium* colonization and reducing pathogenic activity, and speculate that low HM/BF prevalence could contribute to gut dysbiosis in the context of CHD.[64] The authors propose *Bifidobacterium* and oligosaccharide supplementation for infants with critical CHD, but stop short of recommending improved lactation support for these infants and their families as a mechanism to promote intestinal homeostasis. Of the remaining abstracts,[69] studies,[65,67,68] or reviews[66] identified on the topic of the gut microbiome in patients with CHD, only one briefly mentions HM/BF[68] and none discuss HM/BF as a therapeutic intervention for gut dysbiosis.

The omission of HM/BF from the CHD gut microbiome literature is not entirely surprising as support for HM/BF in the CHD population has been historically inadequate and under prioritized by the healthcare team,[14,70–72] contributing to extremely low prevalence of these feeding practices.[12] We also speculate that, as the underlying cause of cardiac NEC may be different than in preterm infants, some providers might assume that HM is not similarly protective for infants with CHD. Both Huang et al.'s[64] novel research demonstrating similarities between the gut microbiome of preterm infants and those with critical CHD and our findings of strong associations between HM and reduced NEC would discount this assumption. Furthermore, in animal studies focused on the mechanistic relationship between HM and preterm NEC, a common method of NEC–induction involves subjecting mice to hypoxia, infant formula, and introduction of lipopolysaccharide to induce inflammation[73] – a process with clear analogies to the SV CHD clinical course. Infants with SV CHD and their lactating parents also experience many of the same risk factors for gut dysbiosis as in preterm birth (eg, antibiotic use, delayed fetal development, formula supplementation, lack of direct BF, breast pump use).[60,74,75] Therefore, there is a critical need for CHD researchers and clinicians to learn from and build upon the foundation of lactation research in preterm populations, with the relationship between HM components/microbiota and infant gut microbiome alterations in the context of critical CHD an important area for future study.

Sepsis and infection

Infants with high HM feeding duration in the S1P hospitalization had lower odds of postoperative sepsis and infection-related complications, while those with high direct BF duration had 100% lower odds of postoperative sepsis. No infants in the interstage high BF group were readmitted for sepsis, although the overall prevalence of interstage sepsis was low. HM has been associated with lower rates of sepsis[16,17,19,30,76,77] and infection[32] for preterm infants and infants with surgical gastrointestinal anomalies, with protective mechanisms likely similar to those previously described for NEC (eg, reduced gut dysbiosis with subsequent lower risk of pathogenic gut bacteria translocation[78]). A 2023 study by Ghosh et al.[79] reported a 2.58 times increase in the odds of postoperative infection (ie, bloodstream infection, surgical site infection, ventilator-associated pneumonia; $p = 0.040$) associated with exclusive infant formula, compared to exclusive HM, for infants undergoing cardiac surgery at a single center in India. This study, however, is limited in that infants in the exclusive HM group were substantially older (ie, median 60 days vs. 15 days) and underwent less complicated procedures, on average. Furthermore, Ghosh and colleagues described COVID-19-related restrictions on maternal bedside presence that may have disproportionately affected infants living in remote areas or families who could not travel, and socioeconomic factors or other social determinants of health were not reported. We identified no studies specifically examining the relationship between direct BF and infection or sepsis in any hospitalized neonates.

Our finding of reduced odds of sepsis in high BF groups offers novel evidence that direct BF as a mode of HM delivery may be particularly beneficial in preventing sepsis in infants with SV CHD. Interestingly, a 2019 study[75] using a robust, multi-method analytical approach identified mode of feeding as a key contributor to the HM microbiome, with HM fed directly from the breast exhibiting significantly decreased pathogenic *Enterobacteriaceae* and *Enterococcaceae*, high beneficial *Bifidobacterium*, and increased microbial richness and diversity compared to expressed HM. There is also emerging evidence

supporting a retrograde inoculation hypothesis, in which the flow of milk from an infant's oral cavity back into the mammary ductal system shapes the microbiome of both the infant and the lactating parent.[75,80–83] This microbial communication between infant and parent during BF could be one mechanism to explain the changes in the immunological composition of HM in response to pathogenic organisms that can lead to sepsis[84] and suggests that direct BF could confer critical protection to vulnerable infants, including those with SV CHD.

Length of stay

Hospital length of stay was consistently lower in the HM and BF groups at all time points examined. Interestingly, infants with exclusive HM preoperatively at S1P had a 13% mean reduction in S1P length of stay. The preoperative time typically lasts less than a week and is followed by high-risk intervention, an often complicated recovery, and a lengthy hospital stay (mean 48 ± 32 days). It is notable that this short exposure to exclusive HM appeared to have lasting impact in our matched cohort.

Similarly, infants with high HM feeding duration in the S1P hospitalization had a 25% lower mean S1P length of stay, and those with high BF duration had a 23% lower mean S1P length of stay. Associations between HM and shorter length of stay have been demonstrated for preterm infants[25,85] and infants with other surgical anomalies,[18,30,77,86] although results are inconsistent, may be dose dependent,[18,30,86] and may differ between MHM[85] and donor HM.[25] To our knowledge, only one study has examined associations between HM and length of stay for infants with CHD. Yu et al.[87] found that infants fed HM had a 3.9 days shorter mean length of stay compared to a formula feeding group in a cohort with varied CHD diagnoses; however, this study exhibits high risk of bias.[15]

We did not identify any studies examining direct BF and length of stay for infants with surgical congenital anomalies. The preterm literature similarly focuses primarily on HM feeding as a nutritional entity rather than on the mode of feeding, although Suberi et al.[88] reported an association between direct BF as the first mode of oral feeding (compared to bottle) for preterm infants and ~1 week earlier NICU

discharge. Our study is unique in that it addresses the critical gap in knowledge about direct BF in this population and suggests some differential benefits.

Establishing causality between HM or BF and S1P length of stay in this population is challenging. Hospital length of stay has often been considered as a predictor of HM/BF practices rather than as an outcome impacted by infant feeding,[89] and the psychological stress of extended hospitalization, postoperative complications, or family/work obligations could impact a parent's ability to provide HM/BF. These are potentially unmeasured confounders that could impact our results, and there is likely some element of multidirectionality between HM/BF and hospital length of stay. An individual infants' hospital stay can be extended for many reasons, and numerous potential disruptions to feeding development have been outlined by Jones et al.[90] However, in light of the limitations of the registry data in this study, our propensity score models included multiple indicators of a complicated clinical course (Table 5.2; eg, preoperative instability, intubation duration, major postoperative procedures) and parental access to supportive resources (eg, insurance type, SDI score of ZCTA, comprehensive parental support delivered), along with clinical site to account for differences in institutional practices, protocols, and level of lactation support. Even when accounting for these potential confounding variables, associations between HM or BF and length of stay remained strong. As a partial explanation, we hypothesize a causal pathway between HM/BF; reduced incidence of NEC, infection, and sepsis; and S1P hospital length of stay.[29]

The potential for a causal effect of HM and/or BF on length of stay is further supported by the results from the S2P hospitalization, in which the temporal relationship between HM/BF and S2P postoperative length of stay was more clearly defined. Once again, length of stay was significantly shorter in all HM/BF groups, with reductions similar in magnitude to those in the S1P analysis (ie, 18%–29%). Multisite, prospective, longitudinal studies with granular feeding data are needed to confirm these results, and future research should also elucidate potential mechanistic causes. Within-site variation, by individual

providers,[91] of practices that impact both HM/BF and length of stay could also be important for future research and potential practice modification. Given that hospital length of stay has been identified as the key driver of hospital costs for infants with CHD,[92] our findings suggest that improving HM/BF prevalence has potential to not only improve the health of infants with SV CHD, but also to reduce economic costs for families, payers, and institutions.

Mortality

While most analyses of all-cause mortality did not reach statistical significance in this study, all estimates were substantially lower in the HM and BF groups. The clinical importance was particularly striking for direct BF groups, with estimates of 75%–100% lower odds of mortality. Previous research in preterm[17,19] and other neonatal surgical populations[18] suggests an association between HM and mortality, and our study provides initial evidence of a potential difference in survival related to HM/BF practices for infants with SV CHD. Regarding direct BF, it may be tempting to assume that infants who are able to BF are less "sick" than those who are not and therefore at lower risk for death; however, the propensity score models for our cohort included many indicators of an infant's relative sickness and previous research has described successful direct BF in the context of severe CHD disease presentation.[14] We speculate that the achievement of the complex neurodevelopmental skill of direct BF could both reflect and promote improved clinical status. Future studies including detailed data on feeding method/dose and reasons for infant death are needed to support more robust survival analyses in this population.

Limitations

Limitations of our study include those inherent in analysis of multisite registries, such as potential for inaccurate, inconsistent, or missing data. While registry data in this rare disease population offers advantages, we could not fully characterize an infant's HM/BF trajectory over time, and the dose could have varied widely within groups. We also did not have information on the timing of outcomes (eg, dates of NEC or sepsis diagnosis). Therefore, although our analytical approach was designed to reduce bias,

results should be interpreted as hypothesis-generating rather than confirmatory. For infants in HM groups, we were unable to determine whether the HM was from the lactating parent or donor HM. It is increasingly clear that MHM and donor HM are not equivalent, as many of the protective bioactive components of MHM are eliminated during pasteurization and the nutritional composition and microbiota differ.[93] Additionally, ~93% of infants with SV CHD are prescribed a high–calorie diet at S1P discharge, often by adding infant formula or bovine-milk-derived fortifier to HM.[12] It is unclear whether an infant fed only HM plus fortification was considered to receive exclusive HM, and it is possible that clinicians at different sites defined exclusive HM differently. Definitions of outcomes (eg, NEC) could also have varied across sites. Analyses of the preoperative time only included the 57.8% of infants who were enterally fed, and the results may not be generalizable to all infants with SV CHD.

Considering the known association between HM/BF and maternal factors such as race and/or economic status, our inclusion of variables derived from an infant's ZCTA are a strength of this study. However, these variables only approximate an individual family's situation. Moreover, we did not have information on maternal intent for HM/BF or factors such as previous BF experience that could impact self-efficacy for these feeding practices. Future multisite, prospective, longitudinal studies with careful measurement of the volume and dose of HM/BF throughout the infant's first year of life should also include detailed analysis of relevant family, maternal, and social factors.

Conclusion

In this large, multisite study using robust statistical techniques designed to reduce bias and support causal inference, we found that infants with high HM feeding and direct BF exposures experienced multiple significant improvements in outcomes for infants with SV CHD, including reduced incidence of NEC, infection, and sepsis; substantially shorter length of stay at both S1P and S2P surgeries; and lower mortality. These results align with previous research including preterm and other surgical neonates; however, HM/BF research in the context of CHD currently lags behind that focused on

preterm populations. Future work is urgently needed to confirm the results of this study and to identify potential mechanistic causal pathways for improved outcomes. Most importantly, this study highlights the critical need for improved, condition-specific lactation support to address the currently low rates of HM and BF for infants with SV CHD. Our findings demonstrate that increasing the dose and duration of HM and direct BF has strong potential to substantially improve the health outcomes of these vulnerable infants.

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Chapter 6: Synthesis

This dissertation research focused on human milk (HM) and direct (BF) for infants with single ventricle congenital heart disease (SV CHD), examining the prevalence of these feeding practices, identifying supportive and limiting factors, and estimating the effect of HM and BF on key outcomes for these vulnerable infants. In this chapter, we summarize and synthesize the primary findings of the dissertation and discuss implications for future research and practice.

Summary of Findings

Chapter 2

In Chapter 2, we systematically reviewed and critiqued the current literature on the relationship between HM feeding and health outcomes for infants with CHD. Following Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines,[1] we screened 446 articles and reviewed 16 that examined the impact of HM on health outcomes for infants with CHD. As a group, we found that the available evidence exhibited a high risk for bias with limitations related to low statistical power, unmet analytical assumptions, and unclear criteria for feeding group assignment (ie, multiple treatment interference). The strongest evidence demonstrated associations between exclusive HM feeding and reduced odds of necrotizing enterocolitis. Additional studies suggested that increased HM dose and/or duration may promote shorter hospital length of stay, improved postoperative nutrition, and improved growth; however, these results had substantial limitations. Moreover, despite the known associations between race, ethnicity, and social determinants of health (eg, family economic status) and infant feeding practices,[2] only 44% of studies reported infant race or ethnicity, and 18% included information on social or economic characteristics of the sample.

Our findings in Chapter 2 highlight the limitations of small, single-site studies in this rare disease population, revealing a need for high-quality, adequately-powered, multisite research. We recommended that future studies incorporate feeding measures that clearly quantify the percentage of maternal HM,

donor HM, infant formula, and milk fortifier received by infants during hospitalization, and clarify the route of nutrition (eg, feeding tube, direct BF). This improved nutritional measurement would support an examination of dose-response differences in outcomes. Finally, we emphasized that future CHD feeding research should report social and familial information, and should examine systematic and institutional contributors to disparities in HM outcomes in this population.

Despite the limitations in the current research, our systematic review identified some probable benefits of a HM diet for infants with CHD, with the strongest evidence indicating that an exclusive HM diet reduces the odds of NEC and potential for additional benefits such as reduced length of stay and improved growth. Considering these findings and given the conclusive benefits of HM feeding for other vulnerable neonatal populations,[3–5] we recommended that clinicians and institutions prioritize efforts to improve HM feeding for infants with CHD, but emphasized the need for future high-quality research on this topic.

Chapter 3

In Chapter 3, we established foundational evidence about the prevalence of HM and direct BF in a national, multisite cohort of infants with SV CHD. To our knowledge, this study is the first in-depth examination of HM and BF for infants with SV CHD – considered the most critical form of the disease; the first to delineate between HM feeding and direct BF for these infants; and the largest study of HM/BF for infants with any form of CHD.

We analyzed data from the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) registry (2016– 2021), which includes more than 2500 infants with SV CHD from 68 pediatric cardiology centers across the United States (US). We examined three feeding outcomes (ie, any HM feeding; exclusive HM feeding; and any direct BF) at four time points: Preoperatively at the neonatal stage 1 palliation (S1P) surgery/intervention; at S1P discharge; at the subsequent stage 2 palliation (S2P) surgery/intervention; and at S2P discharge. We found that, for 2491 infants with SV CHD, the prevalence

of HM and BF was lower than global and national recommendations, lower than the US population average, and declined over time. For example, 37.1% of infants with SV CHD were receiving any HM feeding at S2P (median 4.8 months old), compared to the US population average of 55.8% any HM feeding at 6 months old,[6] and only 9.4% of infants with SV CHD had any BF at S2P. However, feeding outcomes varied widely among NPC-QIC sites. For example, the prevalence of both any HM and any BF ranged from 0–100% across sites at S1P discharge, and certain sites had consistently above-average prevalence of HM/BF. These findings suggest that site-specific practices play a significant role in HM and BF outcomes and indicate that there are substantial opportunities for population-level improvement in this area. We recommended that future research identify factors that support or limit HM and BF for these infants, thus highlighting modifiable targets for improvement.

Additionally, in Chapter 3 we found a significant positive association between direct BF at S1P discharge and any HM feeding at the subsequent S2P. These findings underscore the critical need to improve institutional support not only for HM, but also for direct BF during the neonatal hospitalization as a potential means of increasing exposure to the protective benefits of HM and optimizing the health of infants with SV CHD.

Chapter 4

The research presented in Chapter 4 addressed the previously established need to identify variables that support and limit HM and BF for infants with SV CHD. We conducted a secondary analysis of the NPC-QIC registry, focusing on predictors of any HM feeding, exclusive HM feeding, and any direct BF at the S1P discharge (n=1944) and at the time of the S2P surgery/intervention (n=1578). Our machine learning analytical approach involved two rounds of elastic net logistic regression on multiply imputed data to identify key predictors of each feeding practice at each time point.

We found that variables that were significant in the models most frequently belonged to five predictor domains: Preoperative feeding practices; demographics and social determinants of health; the

infant's feeding route at S1P discharge and at S2P; the infant's clinical course, and NPC-QIC site. Given the importance of preoperative feeding variables in predicting later HM and BF outcomes, we identified the preoperative time as a window of opportunity in which to set the stage for the future nutrition of infants with SV CHD. Most notably, any preoperative BF was significantly associated with 2.02 times greater odds of any HM and 3.02 times greater odds of any BF at S1P discharge, with similar results at S2P, while preoperative bottle feeding of any type of nutrition was negatively associated with HM and BF at both time points. These findings lend further support to the implication that institutional support of HM expression without concurrent support for direct BF could contribute to early HM weaning in this population.

We also found that economic indicators (ie, insurance type; residential zip code tabulation area median income) and infant race were significant predictors of HM and BF for infants with SV CHD. These results align with previous research in preterm and healthy infant populations, and highlight health disparities for infants with SV CHD in which not all families have access to resources needed to establish and maintain HM feeding and BF. We discussed the complex possible contributors to these health disparities and emphasized that, in clinical practice, those caring for infants with SV CHD must examine individual and institutional bias that could play a role in disparate infant feeding outcomes.

While the number of NPC-QIC sites (n=67) and the variability in site size (n=1–153) prevented site inclusion in the elastic net logistic regression models, additional analysis involving likelihood ratio tests of models with and without site added determined that NPC-QIC site was a significant predictor of HM and BF outcomes, particularly at the S1P discharge time point. These results aligned with the Chapter 3 findings of wide variation in HM/BF prevalence among NPC-QIC sites. Given that feeding establishment for infants with SV CHD is heavily supervised by healthcare teams, we highlighted the finding that site-specific clinical practices may predict HM/BF outcomes and recommended

implementation and testing of practices (eg, skin-to-skin contact;[7] a multidisciplinary approach to lactation support[8]) that have been shown to support HM and BF in other vulnerable neonatal populations.

To our knowledge, the work presented in Chapter 4 is the first research to examine predictors of HM and BF practices for infants with CHD of any type, and the application of machine learning techniques to CHD infant feeding data is a novel contribution. Our findings elucidated areas of focus for future research and modifiable targets for practice improvement. We recommended that future work focus on the development and testing of family-centered, culturally-sensitive interventions to support HM and BF during the prenatal and S1P preoperative times, as early intervention could be crucial in improving the low prevalence of HM and BF in this population. We noted that these interventions should include evidence-based strategies to address bias and seek to minimize disparities related to social determinants of health.

Chapter 5

In Chapter 5, we presented a manuscript in which we investigated the effect of HM and direct BF on key health outcomes for infants with SV CHD. We hypothesized that higher dose and/or duration of HM and BF would result in reduced prevalence of necrotizing enterocolitis, and that we would identify additional benefits related to infection-related complications, sepsis, time to full feeding volume, hospital length of stay, unplanned hospital readmission, feeding-related hospital readmission, or all-cause mortality. In this final analysis of the NPC-QIC registry, we examined outcomes related to preoperative HM and BF (n=1298); HM and BF dose and duration in the S1P hospitalization (n=1106); HM and BF dose and duration in the interstage period between S1P discharge and S2P (n=1584); and HM and BF at the S2P (n=1849). Our analytical approach involved propensity score matching of multiply imputed data to support causal inference, reduce bias, and determine the average treatment effect among the treated.

We found that, in propensity score matched cohorts, all outcome estimates at four time points during the first year of life were better in high HM and/or BF groups, with many results reaching

statistical significance and substantial clinical significance across the board. Infants with high HM and/or BF had significantly lower odds of preoperative and postoperative necrotizing enterocolitis; lower odds of postoperative sepsis and infection-related complications; and shorter hospital length of stay at both S1P and S2P. While most analyses of all-cause mortality did not reach statistical significance, all point estimates were substantially lower in the HM and BF groups, including estimates of 75%–100% lower odds of mortality related to direct BF. To explain these results, we explored mechanistic causes related to HM components (eg, HM oligosaccharides; maternal immunoglobulin A)[9–11] and the infant gut microbiome,[12,13] and hypothesized a causal pathway in which HM and direct BF reduce the incidence of necrotizing enterocolitis, sepsis, and infection, leading to shorter length of stay.

The findings presented in Chapter 5 address the critical gap in the literature regarding the effect of HM and BF on several key outcomes for infants with SV CHD, and represent the first large, multisite analysis on the topic. To our knowledge, this study is also the first to use methods for causal inference (ie, propensity score matching) in CHD feeding research, and the first to identify specific benefits related to direct BF for infants with any form of CHD. Based on our findings, we noted that future research is needed to replicate these results with high-quality, granular feeding data that allows for examination of HM and BF dose response. This study highlighted the need for improved, condition-specific lactation support to increase the dose and duration of HM and direct BF for infants with SV CHD, with substantial promise to improve health outcomes for these vulnerable infants.

Synthesis and Implications for Future Research and Practice

Taken as a whole, this body of work addresses the critical gap in the literature regarding our understanding of HM and direct BF for infants with SV CHD. Our research overcomes limitations of the current evidence identified in Chapter 2 by analyzing a large, multisite registry with adequate statistical power; using advanced methods involving machine learning and propensity score matching to support causal inference; focusing exclusively on infants with SV CHD to bolster generalizability; and clearly

delineating between HM feeding and direct BF. The research presented in this dissertation is the first broadscale examination of HM and BF for infants with SV CHD and, to our knowledge, the only large, multisite research on HM and BF for any form of CHD.

In Chapter 3, we established foundational evidence that the prevalence of these feeding practices in the US is low and declines over time, although prevalence varied widely among NPC-QIC sites. These findings highlighted the need for further understanding of factors that contribute to the prevalence of HM and BF in this population; therefore, in Chapter 4, we identified predictors that support and limit HM and BF at S1P discharge (~1 month old) and at S2P (~5 months old), with the strongest predictors in the domains of preoperative feeding practices; demographics and social determinants of health; the infant's feeding route at S1P discharge and at S2P; the infant's clinical course; and NPC-QIC site. In Chapter 5, we estimated that the magnitude of the effect of HM and BF on key health outcomes for these infants was substantial, with infants in HM and BF groups experiencing significantly lower odds of necrotizing enterocolitis, sepsis, and infection-related complications; shorter hospital length of stay; and potentially reduced mortality.

Considering the wide variation in HM/BF prevalence among NPC-QIC sites, future research should investigate practices to support lactation that have been implemented by NPC-QIC institutions with above-average prevalence of HM feeding and direct BF. Within-site variation, by individual providers, of practices that impact HM and BF could also be important for future study and potential practice modification. Future work is also needed to explore the lactation-related experiences and needs of racially, culturally, and economically diverse families of infants with CHD, particularly considering our identification of disparities related to demographics and social determinant of health, in which not all families had access to resources needed to establish and maintain HM and BF. Clinically, healthcare teams must interrogate individual and institutional bias that could contribute to infant feeding disparities and work to develop lactation interventions that support equitable HM and BF outcomes.

Our findings of improved outcomes for infants in HM and BF groups should be replicated in multisite, prospective, longitudinal studies with careful measurement of the volume of HM/BF throughout the infant's first year of life to determine dose response; should be expanded to include additional CHD diagnoses; and should include detailed analysis of relevant family, maternal, and social factors (eg, maternal education level; maternal intent to provide HM/BF). Causal mechanisms for improved health outcomes should also be investigated, with the relationship between HM components/microbiota and infant gut microbiome alterations in the context of critical CHD a particularly important area for future study.

Most importantly, the work presented in this dissertation underscores the critical need for future research to develop and test condition-specific, culturally-responsive, family-centered lactation interventions to increase the low prevalence of HM and direct BF for infants with SV CHD as, to our knowledge, no such interventions currently exist. Future research and practice change should focus on the prenatal and early neonatal time points as a window of opportunity to set the stage for the future nutrition of these infants. Additionally, interventions should support not only HM feeding, but also establishment of direct BF during the S1P hospitalization, when clinically appropriate, as a means of reducing the odds of early HM weaning.

Conclusion

This dissertation examined HM and BF for infants with SV CHD in the large, multisite NPC-QIC registry. We found that the prevalence of HM and BF is low in this population but that infants who were able to establish direct BF by the neonatal S1P discharge had greater odds of maintaining HM feeding at the subsequent S2P surgery/palliation. We used a machine learning approach to identify supportive and limiting predictors of HM and BF, with factors in the domains of preoperative feeding practices; demographics and social determinants of health; the infant's route of feeding at S1P discharge and at S2P; the infant's clinical course; and NPC-QIC site emerging as the strongest predictors. In propensity score

matched cohorts, we determined that infants in high HM and BF groups had significantly improved outcomes related to necrotizing enterocolitis; sepsis and infection; length of stay; and mortality. Future work is needed to replicate these results with high-quality granular feeding data and in broader CHD populations, and to develop and test interventions designed to support HM and BF in this vulnerable population. Such interventions have strong potential to improve the health and development of infants with SV CHD.

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Journal of Pediatrics Editorial Office (ELS) <jpedsedoffice@elsevier.com> Sun, Jul 2, 2023 at 11:31 PM
To: Kristin Elgersma <elger005@umn.edu>

Dear Dr. Elgersma,

Many thanks for writing to us.

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Thank you very much.

Best regards,

Akshay

Akshay K Nair

Editorial Office

Journal of Pediatrics

From: Kristin Elgersma <elger005@umn.edu>
Sent: Saturday, July 1, 2023 11:01 PM
To: Journal of Pediatrics Editorial Office (ELS) <jpedsedoffice@elsevier.com>
Subject: Permission for manuscript in dissertation

Hello,

I am writing in regard to a recently accepted manuscript in *The Journal of Pediatrics:*

Elgersma KM, Wolfson J, Fulkerson JA, et al. Predictors of human milk feeding and direct breastfeeding for infants with single ventricle congenital heart disease: Machine learning analysis of the National Pediatric Cardiology Quality Improvement Collaborative registry. J Pediatr. Published online June 2023:113562. doi:10.1016/j.jpeds.2023.113562

I am currently a PhD candidate at the University of Minnesota, and I would like to include the Accepted Manuscript version of this manuscript in my dissertation, which I will defend this summer. Post-graduation, my dissertation will go into a digital conservancy hosted at the University of Minnesota, but would be under embargo (not publically available) until the summer of 2025, which appears to fulfill the 12-month requirement for the journal. In looking at the Author Agreement, this seems to be acceptable:

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Could you please confirm if including this article in my dissertation (along with an acknowledgment of publication and doi link to the full version) and thus the electronic repository at my institution is acceptable?

Thank you very much,

Kristin Elgersma

Appendix B. Institutional Review Board Approval

UNIVERSITY OF MINNESOTA

Twin Cities Campus

Human Research Protection Program
Office of the Vice President for Research

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200 Oak Street S.E.
Minneapolis, MN 55455

612-626-5654
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EXEMPTION DETERMINATION

July 21, 2021

Anne McKechnie

612-624-6491
acmckech@umn.edu

Dear Anne McKechnie:

On 7/21/2021, the IRB reviewed the following submission:

Type of Review:	Initial Study
Title of Study:	Human Milk and Direct Breastfeeding for Infants with Single Ventricle Congenital Heart Disease: An Analysis of Incidence, Supportive Factors, and Impact on Key Outcomes
Investigator:	Anne McKechnie
IRB ID:	STUDY00013371
Sponsored Funding:	None
Grant ID/Con Number:	None
Internal UMN Funding:	None
Fund Management Outside University:	None
IND, IDE, or HDE:	None
Documents Reviewed with this Submission:	• List of requested variables, Category: Other; • Fairview Approval, Category: Fairview Approval; • NPC-QIC Data Form, Category: Other; • Elgersma HRP-595 - NPCQIC protocol.docx, Category: IRB Protocol;

The IRB determined that this study meets the criteria for exemption from IRB review. To arrive at this determination, the IRB used "WORKSHEET: Exemption (HRP-312)." If

you have any questions about this determination, please review that Worksheet in the HRPP Toolkit Library and contact the IRB office if needed.

This study met the following category for exemption:

• (4) Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met: (i) The identifiable private information or identifiable biospecimens are publicly available; (ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects; (iii) The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or (iv) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.

Ongoing IRB review and approval for this study is not required; however, this determination applies only to the activities described in the IRB submission and does not apply should any changes be made. If changes are made and there are questions about whether these activities impact the exempt determination, please submit a Modification to the IRB for a determination.

In conducting this study, you are required to follow the requirements listed in the Investigator Manual (HRP-103), which can be found by navigating to the HRPP Toolkit Library on the IRB website.

For grant certification purposes, you will need these dates and the Assurance of Compliance number which is FWA00000312 (Fairview Health Systems Research FWA00000325, Gillette Children's Specialty Healthcare FWA00004003).

Sincerely,

Zenab Tiamiyu

IRB Analyst

Appendix C: Supplementary Material for Manuscript #1

Variables Included in Imputed Data Sets

1. Fetal diagnosis
2. No parental prenatal support
3. Comprehensive parental prenatal support
4. Birth year
5. NPC-QIC site
6. Sex
7. Race
8. Ethnicity
9. Born at the NPC-QIC center
10. Birth WAZ
11. Preterm <37 weeks
12. Age at S1P admission
13. Insurance type
14. Rural-urban commuting area of ZCTA
15. Median income of ZCTA
16. Social deprivation index of ZCTA
17. Primary cardiac diagnosis
18. Secondary cardiac diagnosis
19. Genetic syndrome
20. Other major congenital anomaly
21. No postnatal parental support
22. Comprehensive postnatal parental support
23. S1P preoperative instability
24. S1P preoperative enteral feeding
25. S1P preoperative feeding types: breastfeeding, bottle with formula, bottle with human milk, NG trophic, and/or NG > trophic
26. Type of S1P preoperative NG nutrition (human milk, formula, combination)
27. S1P preoperative necrotizing enterocolitis
28. Age at S1P
29. WAZ at S1P
30. LAZ at S1P
31. Breathing spontaneously at S1P
32. S1P type
33. No circulatory arrest, cardiopulmonary bypass, or cross clamp during S1P
34. Had S1P cardiopulmonary bypass
35. Had S1P cross clamp
36. S1P cardiopulmonary bypass duration
37. S1P cross clamp duration
38. Used ECMO in the operating room
39. S1P postoperative ECMO
40. S1P delayed sternal wound closure
41. Need for one or more cardiac reoperations post S1P
42. S1P postoperative intubation duration
43. Need for reintubation within 48 hours after initial postoperative extubation
44. S1P postoperative complications
45. S1P postoperative necrotizing enterocolitis
46. S1P postoperative infection-related complication
47. S1P postoperative sepsis
48. No major S1P postoperative procedures

49. S1P postoperative laryngoscopy
50. S1P postoperative bronchoscopy
51. S1P postoperative cardioversion
52. S1P postoperative dialysis
53. S1P postoperative diaphragm plication
54. S1P postoperative fundoplication
55. S1P postoperative procedure for G-tube
56. S1P postoperative pericardiocentesis
57. S1P postoperative thoracic duct ligation
58. S1P postoperative tracheostomy
59. Weaned inotropes/vasoactive meds within 5 days postoperatively
60. S1P postoperative days to enteral feeds
61. S1P postoperative days to full feeds
62. Parent 24 hour room-in care prior to S1P discharge
63. S1P length of stay
64. Discharged after S1P
65. # of cardiac meds at S1P discharge
66. Oxygen saturation at S1P discharge
67. Ventricular Function at S1P discharge
68. Tricuspid/Systemic AV Valve Regurgitation at S1P discharge
69. Neo-Aortic Valve Regurgitation at S1P discharge
70. Aortic arch obstruction at S1P discharge
71. WAZ at S1P discharge
72. LAZ at S1P discharge
73. Fortification at S1P discharge
74. S1P discharge feeding route: G-tube, NG tube, breastfeeding, and/or bottle feeding
75. S1P discharge nutrition type (human milk, formula, combination)
76. S1P discharge status (to home, inpatient until S2P, early exit from registry, etc.)
77. # of unplanned interstage readmissions
78. Interstage admission for adverse event
79. # of interstage admissions for adverse event
80. # of interstage admissions for adverse event
81. Interstage admission for adverse event: Aspiration
82. Interstage admission for adverse event: Cardiac arrest
83. Interstage admission for adverse event: Infection requiring IV antibiotics
84. Interstage admission for adverse event: Shunt occlusion
85. Interstage admission for adverse event: Life-threatening arrhythmia requiring DC cardioversion
86. Interstage admission for adverse event: Seizure
87. Interstage admission for adverse event: Stroke
88. Interstage admission diagnosis: Altered mental status
89. Interstage admission diagnosis: Arrhythmia
90. Interstage admission diagnosis: Bloody stools
91. Interstage admission diagnosis: Bronchiolitis/Pneumonia
92. Interstage admission diagnosis: Cyanosis/Hypoxia
93. Interstage admission diagnosis: Fussiness
94. Interstage admission diagnosis: GERD
95. Interstage admission diagnosis: Inadequate weight gain
96. Interstage admission diagnosis: Pleural/Pericardial effusion
97. Interstage admission diagnosis: Procedure for residual lesion
98. Interstage admission diagnosis: Respiratory distress
99. Interstage admission diagnosis: Sepsis
100. Interstage admission diagnosis: Stroke
101. Interstage admission diagnosis: Vomiting/Diarrhea

102. Interstage admission diagnosis: Worsening ventricular function
103. Interstage admission diagnosis: Wound infection/Dehiscence
104. Interstage admission diagnosis: Other
105. Interstage major procedure
106. # of interstage major procedures
107. Interstage major procedure: Bronchoscopy
108. Interstage major procedure: Cardioversion
109. Interstage major procedure: Dialysis
110. Interstage major procedure: Diaphragm plication
111. Interstage major procedure: Fundoplication
112. Interstage major procedure: G-tube
113. Interstage major procedure: Pericardiocentesis
114. Interstage major procedure: Peritoneal Drain
115. Interstage major procedure: Placed on ECMO
116. Interstage major procedure: Thoracentesis
117. Interstage major procedure: Thoracic duct ligation
118. Interstage major procedure: Tracheostomy
119. Interstage major procedure: Other
120. Interstage cardiac operation
121. Age at S2P admission
122. WAZ at S2P
123. LAZ at S2P
124. S2P feeding route: G-tube, NG tube, breastfeeding, and/or bottle feeding
125. S2P nutrition type (human milk, formula, combination; total parenteral nutrition)
126. Oxygen saturation at S2P
127. Ventricular Function at S2P
128. Tricuspid/Systemic AV Valve Regurgitation at S2P
129. Neo-Aortic Valve Regurgitation at S2P
130. Aortic arch obstruction at S2P
131. S2P type
132. Had S2P cerebral perfusion
133. Had S2P circulatory arrest
134. Had S2P cardiopulmonary bypass
135. Had S2P cross clamp
136. S2P cerebral perfusion duration
137. S2P circulatory arrest duration
138. S2P cardiopulmonary bypass duration
139. S2P cross clamp duration
140. S2P postoperative ECMO
141. S2P postoperative intubation duration
142. S2P postoperative instability
143. S2P postoperative infection-related complication
144. S2P postoperative sepsis
145. S2P postoperative cardiac arrest
146. Need for one or more cardiac reoperations post S2P
147. No major S2P postoperative procedures
148. S2P postoperative bronchoscopy
149. S2P postoperative cardioversion
150. S2P postoperative dialysis
151. S2P postoperative diaphragm plication
152. S2P postoperative fundoplication
153. S2P postoperative procedure for G-tube
154. S2P postoperative pericardiocentesis

155. S2P postoperative peritoneal drain
156. S2P postoperative thoracentesis
157. S2P postoperative thoracic duct ligation
158. S2P postoperative tracheostomy
159. Other S2P postop procedure
160. Age at S2P discharge
161. WAZ at S2P discharge
162. LAZ at S2P discharge
163. # of cardiac meds at S2P discharge
164. Oxygen saturation at S2P discharge
165. Ventricular Function at S2P discharge
166. Tricuspid/Systemic AV Valve Regurgitation at S2P discharge
167. Neo-Aortic Valve Regurgitation at S2P discharge
168. S2P discharge feeding route: G-tube, NG tube, breastfeeding, and/or bottle feeding
169. S2P postoperative length of stay
170. S2P discharge status (to home, inpatient until S2P, early exit from registry, etc.)
171. Reason for early exit from registry
172. All-cause mortality

Abbreviations: AV = atrioventricular valve; DC = direct current; ECMO = extracorporeal membrane oxygenation; G-tube = gastrostomy; GERD = gastroesophageal reflux disease; LAZ = length-for-age z-score; NG = nasogastric; NPC-QIC = National Pediatric Cardiology Quality Improvement Collaborative; S1P = stage 1 palliation; S2P = stage 2 palliation; WAZ = weight-for-age z-score; ZCTA = zip code tabulation area.

Appendix D. Supplementary Material for Manuscript #3

Sensitivity Analyses

D.1 Average Treatment Effect Among the Treated of Exclusive Human Milk Feeding and Any Direct Breastfeeding During the Stage 1 Palliation Preoperative Time for Key Outcomes Using Inverse Probability Weighting

Exclusive HM (n=934) vs. Not exclusive HM (n=331)			
	OR or RR	**95% CI**	**p value**
Outcome			
Preop NEC	0.42[a]	(0.19–0.94)	**0.034**
S1P hospital LOS	0.87[b]	(0.77–0.98)	**0.025**
All-cause mortality[c]	0.68[a]	(0.44–1.06)	0.089
Any DBF (n=378) vs. No DBF (n=920)			
	OR or RR	**95% CI**	**p value**
Outcome			
Preop NEC	0.67[a]	(0.26–1.73)	0.413
S1P hospital LOS	0.92[b]	(0.83–1.02)	0.117
All-cause mortality[c]	0.76[a]	(0.48–1.19)	0.229

Abbreviations: CI = confidence interval; DBF = direct breastfeeding; HM = human milk; LOS = length of stay; OR = odds ratio; NEC = necrotizing enterocolitis; preop = preoperative; RR = rate ratio.
[a]Analysis included logistic regression; estimate presented as odds ratio.
[b]Analysis included Poisson regression; estimate presented as rate ratio.
[c]Between stage 1 palliation and 1 year of age.

D.2. Average Treatment Effect Among the Treated of High Human Milk Feeding or Direct Breastfeeding Duration in the Stage 1 Palliation Hospitalization for Key Outcomes Using Inverse Probability Weighting

High HM duration: Exclusive preop HM + any HM at discharge (n=603) vs. Low HM duration: Any type of preop feeding but no HM at discharge (n=464)	**OR or RR**	**95% CI**	**p value**
Outcome			
Postop NEC	0.23[a]	(0.12–0.45)	**<0.001**
Infection-related postop complication[c]	0.51[a]	(0.29–0.92)	**0.024**
Postop sepsis	0.33[a]	(0.16–0.68)	**0.003**
Time to full feeds	0.93[b]	(0.80–1.07)	0.312
S1P hospital LOS	0.75[b]	(0.67–0.83)	**<0.001**
All-cause mortality[d]	0.61[a]	(0.24–1.51)	0.280
High DBF duration: Any preop DBF + any DBF at discharge (n=102) vs. Low DBF duration: Any type of preop feeding but no DBF at discharge (n=1004)	**OR or RR**	**95% CI**	**p value**
Outcome			
Postop NEC	0.70[a]	(0.31–1.57)	0.383
Infection-related postop complication[c]	0.68[a]	(0.23–1.98)	0.477
Postop sepsis	0.00[a]	NC[e]	**<0.001**
Time to full feeds	0.87[b]	(0.67–1.12)	0.278
S1P hospital LOS	0.79[b]	(0.68–0.91)	**0.001**
All-cause mortality[d]	0.28[a]	(0.03–2.27)	0.231

Abbreviations: CI = confidence interval; DBF = direct breastfeeding; HM = human milk; LOS = length of stay; NEC = necrotizing enterocolitis; OR = odds ratio; postop = postoperative; preop = preoperative; RR = rate ratio; S1P = stage 1 palliation.

[a]Analysis included logistic regression; estimate presented as odds ratio.

[b]Analysis included Poisson regression; estimate presented as rate ratio.

[c]Includes postoperative pneumonia, sepsis, and wound infection.

[d]Between stage 1 palliation and 1 year of age.

[e]Due to rare occurrence of the outcome, confidence intervals were not computable.

D.3. Average Treatment Effect Among the Treated of High Interstage Human Milk Feeding or Direct Breastfeeding Duration (Stage 1 Palliation Discharge to Stage 2 Palliation) for Key Outcomes Using Inverse Probability Weighting

High interstage HM duration: Any HM at S1P discharge + any HM at S2P (n=428) vs. Low interstage HM duration: No HM at S1P discharge + no HM at S2P (n=408)

	OR or RR	95% CI	p value
Outcome			
# of unplanned interstage readmissions	0.95[a]	(0.73–1.22)	0.666
Any interstage readmission for adverse events[c]	0.87[b]	(0.53–1.42)	0.568
Infection-related interstage readmission[d]	0.79[b]	(0.29–1.96)	0.634
Feeding-related interstage readmission[e]	0.64[b]	(0.31–1.34)	0.238
All-cause mortality[f]	0.32[b]	(0.04–2.58)	0.282

High interstage DBF duration: Any DBF at S1P discharge + any DBF at S2P (n=102) vs. Low interstage DBF duration: No DBF at S1P discharge + no DBF at S2P (n=1281)

	OR or RR	95% CI	p value
Outcome			
# of unplanned interstage readmissions	0.81[a]	(0.54–1.20)	0.285
Any interstage readmission for adverse events[c]	0.94[b]	(0.55–1.63)	0.834
Infection-related interstage readmissiond	1.22[b]	(0.67–5.01)	0.706
Feeding-related interstage readmission[e]	0.40[b]	(0.18–0.91)	**0.029**
All-cause mortality[f]	0.00[b]	NC[g]	**<0.001**

Abbreviations: CI = confidence interval; DBF = direct breastfeeding; HM = human milk feeding; OR = odds ratio; RR = rate ratio; S1P = stage 1 palliation; S2P = stage 2 palliation

[a]Analysis included Poisson regression; estimate presented as rate ratio

[b]Analysis included logistic regression; estimate presented as odds ratio

[c]Includes aspiration, cardiac arrest, infection requiring intravenous antibiotics, cardiac shunt occlusion, life-threatening arrhythmia requiring cardioversion, seizure, and stroke

dIncludes pneumonia, sepsis, wound infection/dehiscence, and infection requiring intravenous antibiotics

[e]Includes gastroesophageal reflux disease, bloody stool, poor weight gain, and vomiting/diarrhea

[f]Between stage 2 palliation and 1 year of age

[g]Due to rare occurrence of the outcome, confidence intervals were not computable

D.4. Average Treatment Effect Among the Treated of Human Milk Feeding and Direct Breastfeeding at Stage 2 Palliation for Key Outcomes Using Inverse Probability Weighting

Any HM at S2P (n=785) vs. No HM at S2P (n=1062)			
	OR or RR	**95% CI**	**p value**
Outcome			
Infection-related S2P postop complicationc	0.95[a]	(0.57–1.59)	0.836
S2P postop sepsis	0.60[a]	(0.30–1.22)	0.161
S2P hospital LOS	0.82[b]	(0.69–0.97)	**0.023**
All-cause mortality[d]	0.87[a]	(0.45–1.68)	0.671
Exclusive HM at S2P (n=130) vs. No HM at S2P (n=947)			
	OR or RR	**95% CI**	**p value**
Outcome			
Infection-related S2P postop complicationc	0.66[a]	(0.22–2.00)	0.458
S2P postop sepsis	0.51[a]	(0.14–1.88)	0.309
S2P hospital LOS	0.74[b]	(0.56–0.98)	**0.037**
All-cause mortality[d]	0.58[a]	(0.20–1.72)	0.328
Any DBF at S2P (n=173) vs. No DBF at S2P (n=1674)			
	OR or RR	**95% CI**	**p value**
Outcome			
Infection-related S2P postop complicationc	0.41[a]	(0.12–1.37)	0.147
S2P postop sepsis	0.91[a]	(0.21–3.98)	0.898
S2P hospital LOS	0.71[b]	(0.58–0.88)	**0.001**
All-cause mortality[d]	0.26[a]	(0.03–1.99)	0.195

Abbreviations: CI = confidence interval; DBF = direct breastfeeding; HM = human milk feeding; LOS = length of stay; NEC = necrotizing enterocolitis; postop = postoperative; OR = odds ratio; RR = rate ratio; S2P = stage 2 palliation

[a]Analysis included logistic regression; estimate presented as odds ratio

[b]Analysis included Poisson regression; estimate presented as rate ratio

[c]Includes postoperative pneumonia, sepsis, and wound infection

[d]Between stage 2 palliation and 1 year of age

D.5. Average Treatment Effect Among the Treated of High Human Milk Feeding or Direct Breastfeeding Duration in the Stage 1 Palliation Hospitalization on Key Outcomes in Propensity Score Matched Cohorts, with Restricted Baseline Covariates[a] in the Propensity Score Models

High HM duration: Exclusive preop HM + any HM at discharge (n=603) vs.
Low HM duration: Any type of preop feeding but no HM at discharge (n=464)

	estimate (OR, RR, or β)	(SE)	95% CI	p value
Outcome				
Postop NEC	0.25[b]	–	(0.14–0.44)	**<0.001**
Infection-related postop complication[e]	0.42[b]	–	(0.23–0.80)	**0.008**
Postop sepsis	0.27[b]	–	(0.12–0.59)	**0.001**
Time to full feeds	0.89[c]	–	(0.77–1.03)	0.104
Time to full feeds (days)	-1.61[d]	1.02	(-3.61–0.38)	0.113
S1P hospital LOS	0.70[c]	–	(0.63–0.77)	**<0.001**
S1P hospital LOS (days)	-16.89[d]	2.72	(-22.23– -11.55)	**<0.001**
All-cause mortality[f]	0.60[b]	–	(0.25–1.43)	0.247

High DBF duration: Any preop DBF + any DBF at discharge (n=102) vs.
Low DBF duration: Any type of preop feeding but no DBF at discharge (n=1004)

	estimate (OR, RR, or β)	(SE)	95% CI	p value
Outcome				
Postop NEC	0.61[b]	–	(0.26–1.41)	0.245
Infection-related postop complication[e]	0.51[b]	–	(0.17–1.53)	0.226
Postop sepsis	0.00[b]	–	NC[g]	**<0.001**
Time to full feeds	0.80[c]	–	(0.63–1.01)	0.058
Time to full feeds (days)	-3.06[d]	1.59	(-6.19–0.07)	0.055
S1P hospital LOS	0.66[c]	–	(0.56–0.77)	**<0.001**
S1P hospital LOS (days)	-17.87[d]	3.74	(-25.22– -10.53)	**<0.001**
All-cause mortality[f]	0.33[b]	–	(0.04–2.84)	0.314

Abbreviations: CI = confidence interval; DBF = direct breastfeeding; HM = human milk feeding; LOS = length of stay; NEC = necrotizing enterocolitis; postop = postoperative; preop = preoperative; RUCA = rural-urban commuting area; S1P = stage 1 palliation; SE = standard error; ZCTA = zip code tabulation area

[a]Baseline covariates included prematurity <37 weeks, race, Hispanic/Latinx ethnicity, insurance type, median income of ZCTA, SDI score of ZCTA, RUCA of ZCTA, age at S1P admission, WAZ at birth, primary & secondary cardiac diagnoses, other major anomalies, major genetic syndrome

[b]Analysis included logistic regression; estimate presented as odds ratio

[c]Analysis included Poisson regression; estimate presented as rate ratio

[d]Analysis included linear regression; estimate presented as β

[e]Includes postoperative pneumonia, sepsis, and wound infection

[f]Between stage 1 palliation and 1 year of age

[g]Due to rare occurrence of the outcome, confidence intervals were not computable

D.6. Average Treatment Effect Among the Treated of Human Milk Feeding and Direct Breastfeeding Exposures from Stage 1 Palliation Hospitalization to Stage 2 Palliation for Key Outcomes in Propensity Score Matched Cohorts, Using Generalized Linear Models with a Gaussian Distribution

	β	(SE)	95% CI	p value
S1P preop: Exclusive HM				
S1P hospital LOS (days)	-7.61	4.05	(-15.61–0.38)	0.062
S1P preop: Any DBF				
S1P hospital LOS (days)	-2.94	3.28	(-9.41–3.54)	0.372
S1P hospitalization: High HM duration				
Time to full feeds (days)	-0.68	1.00	(-2.65–1.28)	0.495
S1P hospital LOS (days)	-12.84	3.38	(-19.48– -6.20)	**<0.001**
S1P hospitalization: High DBF duration				
Time to full feeds (days)	-1.96	1.65	(-5.21–1.30)	0.237
S1P hospital LOS (days)	-10.13	3.11	(-16.26– -4.00)	**0.001**
Interstage: High HM duration				
# of unplanned interstage readmissions	-0.02	0.12	(-0.25–0.20)	0.836
Interstage: High DBF duration				
# of unplanned interstage readmissions	-0.09	0.14	(-0.37–0.18)	0.507
At S2P: Any HM				
S2P hospital LOS (days)	-3.78	1.65	(-7.02– -0.55)	**0.022**
At S2P: Exclusive HM				
S2P hospital LOS (days)	-4.47	2.28	(-8.96–0.02)	0.051
At S2P: Any DBF				
S2P hospital LOS (days)	-4.98	1.71	(-8.36– -1.61)	**0.004**

Abbreviations: CI = confidence interval; DBF = direct breastfeeding; HM = human milk; LOS = length of stay; preop = preoperative; S1P = stage 1 palliation; S2P = stage 2 palliation; SE = standard error