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ORIGINAL RESEARCH

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

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BACKGROUND: Infants with single ventricle congenital heart disease undergo 3 staged surgeries/interventions, with risk for morbidity and mortality. We estimated the effect of human milk (HM) and direct breastfeeding on outcomes including necrotizing enterocolitis, infection-related complications, length of stay, and mortality.

METHODS AND RESULTS: We analyzed the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) registry (2016–2021), examining HM/breastfeeding groups during stage 1 and stage 2 palliations. We calculated propensity scores for feeding exposures, then fitted Poisson and logistic regression models to compare outcomes between propensity-matched cohorts. Participants included 2491 infants (68 sites). Estimates for all outcomes were better in HM/breastfeeding groups. Infants fed exclusive HM before stage 1 palliation (S1P) had lower odds of preoperative necrotizing enterocolitis (odds ratio [OR], 0.37 [95% CI, 0.17–0.84]; *P*=0.017) and shorter S1P length of stay (rate ratio [RR], 0.87 [95% CI, 0.78–0.98]; *P*=0.027). During the S1P hospitalization, infants with high HM had lower odds of postoperative necrotizing enterocolitis (OR, 0.28 [95% CI, 0.15–0.50]; *P*<0.001) and sepsis (OR, 0.29 [95% CI, 0.13–0.65]; *P*=0.003), and shorter S1P length of stay (RR, 0.75 [95% CI, 0.66–0.86]; *P*<0.001). At stage 2 palliation, infants with any HM (RR, 0.82 [95% CI, 0.69–0.97]; *P*=0.018) and any breastfeeding (RR, 0.71 [95% CI, 0.57–0.89]; *P*=0.003) experienced shorter length of stay.

CONCLUSIONS: Infants with single ventricle congenital heart disease in high-HM and breastfeeding groups experienced multiple significantly better outcomes. Given our findings of improved health, strategies to increase the rates of HM/breastfeeding in these patients should be implemented. Future research should replicate these findings with granular feeding data and in broader congenital heart disease populations, and should examine mechanisms (eg, HM components, microbiome) by which HM/breastfeeding benefits these infants.

Key Words: breast feeding ■ congenital heart defects ■ hypoplastic left heart syndrome ■ human milk ■ infant

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CLINICAL PERSPECTIVE

What Is New?

- This is the first large multisite study examining the impact of human milk and breastfeeding on outcomes for infants with single ventricle congenital heart disease.
- All outcome estimates were better in high-human milk and breastfeeding groups, with significantly lower odds of necrotizing enterocolitis, sepsis, and infection-related complications, and significantly shorter length of stay at both the neonatal stage 1 palliation and the subsequent stage 2 palliation.
- All estimates of all-cause mortality were substantially lower in human milk and breastfeeding groups, with clinically important estimates of 75% to 100% lower odds of mortality in direct breastfeeding groups.

What Are the Clinical Implications?

- There is a critical need for improved, condition-specific lactation support to address the low prevalence of human milk and breastfeeding for infants with single ventricle congenital heart disease.
- Increasing the dose and duration of human milk and direct breastfeeding has strong potential to substantially improve the health outcomes of these vulnerable infants.

Nonstandard Abbreviations and Acronyms

HM	human milk
NPC-QIC	National Pediatric Cardiology Quality Improvement Collaborative
S1P	stage 1 palliation
S2P	stage 2 palliation
SDI	social deprivation index
SV	single ventricle

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 US birth defects.[5] Mortality rates have been reduced by up to 38% over the past 4 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 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 breastfeeding are essential to developmental care for infants with critical CHD.[9]

Yet, the SV CHD population has a prevalence[12] of 7% exclusive HM and 9.4% any direct breastfeeding at approximately 5 months of age, 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 breastfeeding 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/breastfeeding for infants with critical CHD diagnoses including SV CHD.[14]

Inadequate lactation support could be reflective of limited evidence about HM/breastfeeding for this population.[9,15] Human milk and breastfeeding 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 breastfeeding 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% to 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 1 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 breastfeeding and outcomes for infants with CHD of any type. Thus, there is a critical gap in knowledge about HM/breastfeeding for infants with SV CHD.

To address this gap in knowledge, we aimed to estimate the effect of HM feeding and direct breastfeeding on key outcomes in a large multisite cohort of infants with SV CHD. We hypothesized that higher dose and/or duration of HM/breastfeeding 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

The data that support the findings of this study are not publicly available. Guidelines for data access by qualified researchers trained in human subject confidentiality protocols are available on the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) website (https://www.npcqic.org/researcher-resources). Further information on analytic methods is available from the corresponding author with the permission of the NPC-QIC.

We conducted a propensity score-matched cohort analysis of data from the NPC-QIC registry (2016–2021), 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. 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] The first author had full access to all data for the study and was responsible for data integrity and analysis.

For this study, infants with SV CHD who completed stage 1 palliation (S1P) were included. S1P procedure types included Norwood with Blalock-Thomas-Taussig, central, or right ventricle-to-pulmonary artery shunts; hybrid Norwood; and Damus-Kaye-Stansel connection with Blalock-Thomas-Taussig or right ventricle-to-pulmonary artery shunts. Stage 2 palliation (S2P) procedure types included unilateral or bilateral bidirectional Glenn, comprehensive stage 2 (primary arch reconstruction), hemi-Fontan, or Kawashima.

General exclusion criteria included family choice not to pursue treatment following birth and S1P admission >3 months of age. Reasons for exclusion at each time point varied, and a flow diagram detailing reasons for inclusion and exclusion at each time point can be found in Figure S1. For example, at time points 1 and 2, infants 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). Additionally, at time point 2, which includes both preoperative and S1P discharge data, infants who were never discharged after S1P were excluded, because there were no feeding data captured at the S1P discharge time point variable for these infants. Similarly, at time point 3, which is based on both S1P discharge data and data collected at the time of S2P, infants who were never discharged between S1P and S2P, exited the registry due to death or parental withdrawal before S1P discharge, or never received S2P (eg, referred for heart transplant, management strategy changed to 2 ventricle repair, determined not to be a candidate for S2P) were excluded. At time point 4, infants with no S2P date were excluded because there were no feeding data captured for these infants at this time point.

We assessed feeding exposures and outcomes at 4 time points (Figure). Our definitions of feeding groups, along with NPC-QIC registry feeding measures and time points of interest, can be seen in Table 1. As described in Table 1, at time point 2 we examined a high-HM-duration group, which included infants with exclusive HM preoperatively at S1P who were still receiving any HM at S1P discharge. 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 with infants who received any type of preoperative feeding but

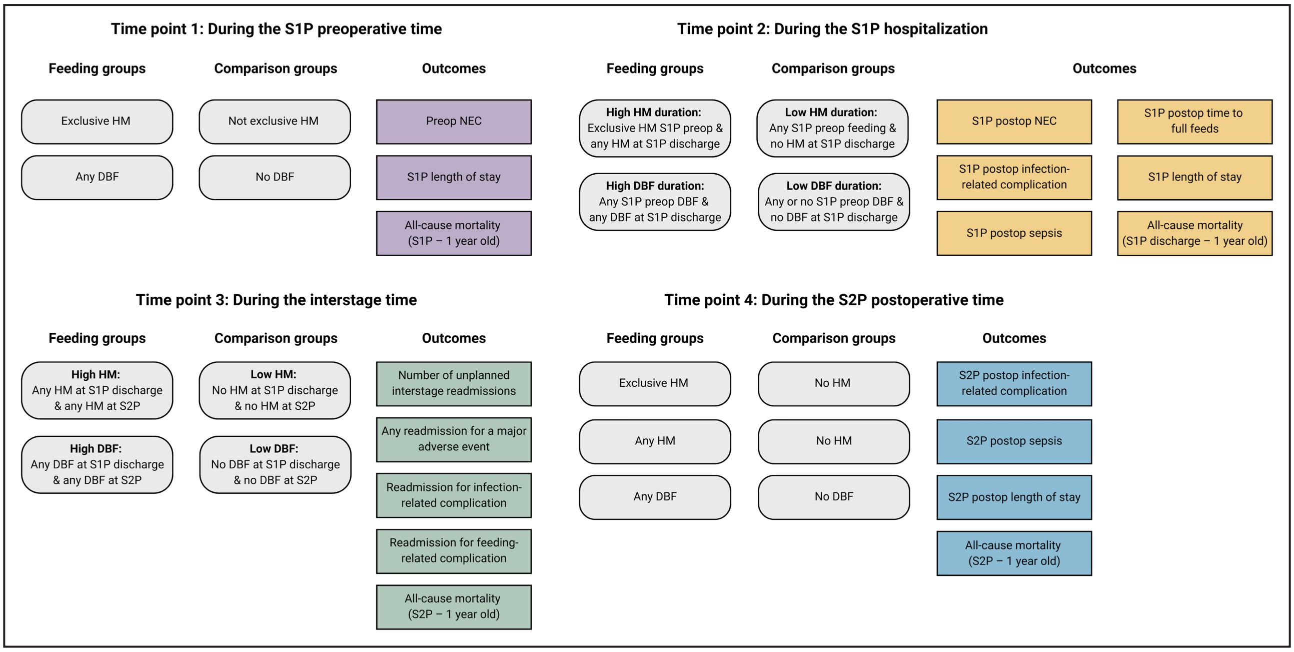

Figure. Feeding groups, outcomes, and time points examined.
DBF indicates direct breastfeeding; HM, human milk; NEC, necrotizing enterocolitis; postop, postoperative; preop, preoperative; S1P, stage 1 palliation; and S2P, stage 2 palliation.

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 breastfeeding and for high- and low-HM/breastfeeding-duration groups across the interstage period.

Outcomes (see Table 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 and length-for-age *Z* scores, and social determinants of health (ie, rural–urban commuting area, median income of residential area, and social deprivation index)[33] has been previously described.[12]

Statistical 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]

We conducted propensity score-matched analyses using the *MatchThem* package[35] for imputed data to determine the average treatment effect among the treated. Propensity score matching supports causal inference with reduced bias and is particularly useful in HM/breastfeeding research, because 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 S1). As recommended by Brookhart et al,[36] variables strongly related to the outcome were included in these models, whereas 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 to 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 absolute standardized mean differences (ie, the largest standardized mean difference for each covariate across imputations[35]), with a standardized mean difference <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 S1, and covariate balance before and after matching is visualized in Figures S2 and S3.

We then 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 (ORs) or rate ratios (RRs) and 95% CIs. 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 additional 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 1 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 average treatment effect among the treated on the same imputed data. Significance was set at $P<0.05$. Following the guidance of Althouse,[43] we did not correct for multiple comparisons, because this analysis of existing data was intended to provide initial evidence in an underexamined area of research and to generate further hypotheses for future confirmation.

Covariate selection for the analyses examining HM or breastfeeding during the S1P hospitalization (Figure, time point 2) was challenging, because 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.

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 2.

The prevalence of HM feeding and direct breastfeeding in the full sample has been previously described.[12] Briefly, during the S1P preoperative time, 49.3% of infants in the full sample received any HM, and 16.1% of infants received any direct breastfeeding. At S1P discharge, the prevalence was 63.4% any HM and 14.4% any direct breastfeeding; at S2P, the prevalence was 37.1% any HM and 9.4% any direct breastfeeding; and at S2P discharge, the prevalence was 9.2% any direct breastfeeding (no HM data were available for the S2P discharge time point).[12]

As visualized in Figure S1, 1298 infants met eligibility criteria for the time point 1 analysis, with 1106 eligible

Table 1. Definitions of Feeding Groups, Outcomes, and Time Points of Outcomes Assessment

NPC-QIC registry measures	Response options	Time point
1. What type of enteral feedings did the patient receive before S1P (in addition to swab to the mouth)? (select all)	• Breastfeeding • Bottle-fed: formula • Bottle-fed: human milk • Did not feed: clinical reasons • Did not feed: institutional practice not to feed patients before S1P • NG tube trophic • NG tube greater than trophic	S1P preop
2. What is the type of feeding via NG tube? (if applicable, select 1)	• Breastmilk • Formula • Combination of breastmilk and formula	S1P preop
3. Route of nutrition recommended in the nutrition plan at discharge (select all)	• G-tube/GJ tube • NG/NJ • Oral: breastfed • Oral: bottle-fed	S1P discharge
4. Type of nutrition recommended in the nutrition plan at discharge (select all)	• Breastmilk • Formula • Combination of breastmilk and formula	S1P discharge
5. Route of nutrition at S2P (select all)	• G-tube/GJ tube • NG/NJ • Oral: breastfed • Oral: bottle-fed • TPN (not feeding)	At S2P
6. Type of nutrition used at S2P (select 1)	• Breastmilk • Formula • Combination of breastmilk and formula	At S2P
7. Route of nutrition recommended in the nutrition plan at discharge (select all)	• G-tube/GJ tube • NG/NJ • Oral: breastfed • Oral: bottle-fed	S2P discharge

Feeding groups examined in this study*	Definition	Time points†
Exclusive human milk	S1P preop: response options selected only include breastfeeding, bottle-fed: human milk, or NG tube (trophic or greater than trophic) with breastmilk selected At S2P: only breastmilk as the type of nutrition selected	Time point 1 Time point 4
Any human milk	S1P preop: response options must include at least 1 of the following: breastfeeding, bottle-fed; human milk; or NG tube (trophic or greater than trophic) with breastmilk selected At S2P: response options can include breastmilk or a combination of breastmilk and formula as the type of nutrition	Time point 1 Time point 4
Any direct breastfeeding	S1P preop: response options must include breastfeeding and can include other options	Time point 1 Time point 4
High-human milk duration in the S1P hospitalization	Exclusive human milk, as defined above, during the S1P preoperative time and any human milk at S1P discharge	Time point 2
Low-human milk duration in the S1P hospitalization	Any type of S1P preop feeding, but no human milk at S1P discharge	Time point 2

(*Continued*)

Table 1. Continued

Feeding groups examined in this study*	Definition	Time points†
High-breastfeeding duration in the S1P hospitalization	Any breastfeeding, as defined above, during the S1P preoperative time and any breastfeeding at S1P discharge	Time point 2
Low-breastfeeding duration in the S1P hospitalization	Any type of S1P preop feeding, but no breastfeeding at S1P discharge	Time point 2
High human milk during the interstage‡	Any human milk, as defined above, at S1P discharge and any human milk at S2P	Time point 3
Low human milk during the interstage	No human milk at S1P discharge and no human milk at S2P	Time point 3
High breastfeeding during the interstage	Any breastfeeding, as defined above, at S1P discharge and any breastfeeding at S2P	Time point 3
Low breastfeeding during the interstage	No breastfeeding at S1P discharge and no breastfeeding at S2P	Time point 3

Outcomes	Definition	Time points†
Necrotizing enterocolitis	Diagnosed per institution, treated medically or surgically	Time point 1 Time point 2
S1P length of stay	Date of admission to date of initial discharge	Time point 1 Time point 2
S2P postop length of stay	Date of S2P to date of initial discharge	Time point 4
Infection-related complication	Diagnosed per institution; aggregate variable including pneumonia, sepsis, or sternal wound infection/dehiscence at all time points; admission requiring IV antibiotics for infection at the interstage time point	Time point 2 Time point 4
Sepsis	Diagnosed per institution	Time point 2 Time point 4
Time to full feeds	Initial postop date on 100 kcal/kg per d enteral feeds	Time point 2
Interstage readmission for feeding-related complication	Diagnosed per institution; aggregate variable including GERD, bloody stool, poor weight gain, or vomiting/diarrhea	Time point 3
No. of unplanned interstage readmissions	Any readmission excluding planned pre-S2P cardiac catheterizations	Time point 3
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	Time point 3
All-cause mortality	Death before first birthday; mortality was assessed following each time point of interest	Time point 1 Time point 2 Time point 3 Time point 4

G-tube indicates gastrostomy tube; GERD, gastroesophageal reflux disease; GJ, gastrojejunal; NG, nasogastric; NJ, nasojejunal; NPC-QIC, National Pediatric Cardiology Quality Improvement Collaborative; postop, postoperative time; preop, preoperative time; S1P, stage 1 palliation; S2P, stage 2 palliation; and TPN, total parenteral nutrition.

*For more details and a visual display of the feeding groups, outcomes, and time points, please see the Figure.

†Time points for the study are as follows:

- Time point 1: during the S1P preoperative time;
- Time point 2: during the S1P hospitalization;
- Time point 3: during the interstage time between S1P and S2P;
- Time point 4: S2P hospitalization.

‡Interstage refers to the time between S1P discharge and S2P.

Table 2. Characteristics and Outcomes of Interest Among the Full National Pediatric Cardiology Quality Improvement Project Registry Sample (N=2491)

Sample characteristics, mean (SD) or n (%)	Value
Sex	
Female	988 (39.7)
Male	1501 (60.3)
Ambiguous or unknown	2 (0.1)
Race	
Another race/multiracial*	297 (12.3)
Black	397 (16.4)
White	1721 (71.3)
Unknown	76
Hispanic or Latino/Latina ethnicity	
Yes	390 (16.4)
No	1987 (83.6)
Unknown	114
Insurance type	
Government	1302 (54.6)
Private/self	1084 (45.4)
Unknown	105
Median income of residential ZCTA	65 667 (23 849)
Unknown	69
SDI score of residential ZCTA	51 (28)
Unknown	63
Rural–urban commuting area	
Metropolitan	1971 (81.1)
Micropolitan	254 (10.5)
Rural	204 (8.4)
Unknown	62
Preterm, <37 wk	
Yes	307 (12.4)
No	2161 (87.6)
Unknown	23
WAZ at birth	−0.18 (1.10)
Unknown	73
Primary cardiac diagnosis	
HLHS	1757 (70.5)
Other SV	734 (29.5)
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 S1P	
Yes	2205 (89.5)
No	259 (10.5)
Unknown or NA	27

Outcomes of interest, mean (SD) or n (%)	
S1P preop NEC	
Yes	58 (2.3)
No	2433 (97.7)
S1P postop NEC	
Yes	324 (13.0)
No	2167 (87.0)
S1P postop infection-related complication†	
Yes	386 (15.5)
No	2105 (84.5)
S1P postop sepsis	
Yes	98 (5.1)
No	1842 (94.9)
Unknown or NA	551
S1P postop time to full feeds, d	16 (17)
Unknown or NA	254
S1P length of stay, d	48 (32)
Unknown or NA	550
No. of unplanned interstage readmissions	1.92 (1.27)
Unknown or NA	1527
Interstage readmission for major adverse event‡	
Yes	67 (7.0)
No	897 (93.0)
Unknown or NA	1527
Interstage readmission for infection-related complication†	
Yes	136 (14.1)
No	828 (85.9)
Unknown or NA	1527
Interstage readmission for feeding-related complication§	
Yes	357 (37.0)
No	607 (63.0)
Unknown or NA	1527

(*Continued*)

Table 2. Continued

Outcomes of interest, mean (SD) or n (%)	
S2P postop infection-related complication[†]	
Yes	107 (5.8)
No	1739 (94.2)
Unknown or NA	645
S2P postop sepsis	
Yes	62 (3.4)
No	1779 (96.6)
Unknown or NA	650
S2P postop LOS	19 (24)
Unknown or NA	758
All-cause mortality[‖]	
Yes	357 (14.3)
No	2134 (85.7)

HLHS indicates 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, SDI, social deprivation index; SV, single ventricle; WAZ, weight-for-age *Z* score; and ZCTA, zip code tabulation area.

[*] 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.

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

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

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

[‖] Between S1P and 1 year of age.

at time point 2, 1584 eligible at time point 3, and 1849 eligible at time point 4. At time point 1, an average of 934 (73.8%) infants across the imputed data sets were in the exclusive HM feeding group and 378 (29.1%) were in the any direct breastfeeding group. At time point 2, 603 (56.5%) infants were in the high-HM-duration group and 102 (9.2%) were in the high-breastfeeding-duration group. At time point 3, there were 428 (51.2%) infants in the high-HM group and 102 (7.4%) in the high-breastfeeding group. At time point 4, there were 785 (42.5%) in the any-HM group, 130 (7.0%) in the exclusive-HM group, and 173 (9.4%) in the any direct-breastfeeding group. Characteristics of the unmatched sample, compared by feeding groups at each time point, can be seen in Tables S2 through S5. The average number of matched and unmatched participants at each time point can be seen in Table S1.

Propensity Score-Matched Analyses

S1P Hospitalization

The estimates for all S1P hospitalization outcomes were better in the high-HM and breastfeeding groups, although not all reached statistical significance (see Tables 3 and 4). 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 [95% CI, 0.78–0.98]; *P*=0.027).

Infants with high-HM-feeding duration across the S1P hospitalization had 72% lower odds of postoperative NEC (OR, 0.28 [95% CI, 0.15–0.50]; *P*<0.001), 52% lower odds of an infection-related postoperative complication (OR, 0.48 [95% CI, 0.25–0.91]; *P*=0.025), 71% lower odds of postoperative sepsis (OR, 0.29 [95% CI, 0.13–0.65]; *P*=0.003), and a 25% reduction in S1P length of stay (RR, 0.75 [95% CI, 0.66–0.86]; *P*<0.001).

Infants with high-direct-breastfeeding 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 [95% CI, 0.02–0.22]; *P*<0.001). In the unmatched cohort, this finding corresponded to 0% versus 6.6% prevalence of S1P postoperative sepsis in the high- versus low-breastfeeding-duration groups. Infants with high-breastfeeding duration also had a 23% reduction in S1P length of stay (RR, 0.77 [95% CI, 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 and 6. Again, the estimates for all outcomes

Table 3. Average Treatment Effect Among the Treated of Exclusive HM Feeding and Any DBF During the S1P Preoperative Time for Key Outcomes in Propensity Score-Matched Cohorts

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

DBF indicates direct breastfeeding; HM, human milk; LOS, length of stay; NEC, necrotizing enterocolitis; OR, odds ratio; preop, preoperative; RR, rate ratio; and S1P, stage 1 palliation.

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

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

[‡] Between S1P and 1 year of age.

[§] $P < 0.05$

Table 4. Average Treatment Effect Among the Treated of High-HM Feeding or DBF Duration in the S1P Hospitalization for Key Outcomes in Propensity Score-Matched Cohorts

Variable	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[*]	(0.15–0.50)	<0.001[¶]
Infection-related postop complication[‡]	0.48[*]	(0.25–0.91)	0.025[¶]
Postop sepsis	0.29[*]	(0.13–0.65)	0.003[¶]
Time to full feeds	0.95[†]	(0.82–1.10)	0.492
S1P hospital LOS	0.75[†]	(0.66–0.86)	<0.001[¶]
All-cause mortality[§]	0.54[*]	(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[*]	(0.29–1.56)	0.355
Infection-related postop complication[‡]	0.66[*]	(0.20–2.21)	0.501
Postop sepsis	0.00[*]	NC[‖]	<0.001[¶]
Time to full feeds	0.89[†]	(0.71–1.12)	0.317
S1P hospital LOS	0.77[†]	(0.66–0.90)	0.001[¶]
All-cause mortality[§]	0.25[*]	(0.03–2.29)	0.218

DBF indicates direct breastfeeding; HM, human milk; LOS, length of stay; NC, not computable; NEC, necrotizing enterocolitis; OR, odds ratio; postop, postoperative; preop, preoperative; RR, rate ratio; and S1P, stage 1 palliation.

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

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

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

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

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

[¶] $P < 0.05$.

were slightly to substantially better in the high-HM and breastfeeding groups. Infants with high-interstage-breastfeeding duration had 100% lower odds of mortality between S2P and 1 year of age in the main analysis, corresponding to 0% versus 3.3% prevalence in high- versus low-breastfeeding groups in the unmatched sample and 77% reduced odds in the bias-corrected analysis (OR, 0.23 [95% CI, 0.09–0.58]; *P*=0.002).

At S2P, all HM/breastfeeding groups had a significant reduction in postoperative hospital length of stay with mean reductions of 18% (RR, 0.82 [95% CI, 0.69–0.97]; *P*=0.018) for any HM, 25% (RR, 0.75 [95% CI, 0.57–0.99]; *P*=0.040) for exclusive HM, and 29% (RR, 0.71 [95% CI, 0.57–0.89]; *P*=0.003) for any breastfeeding.

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 (data not shown, available upon request from the authors).

DISCUSSION

This study addresses a critical gap in knowledge as the first large multisite analysis of the relationship between HM or direct breastfeeding and several key outcomes for infants with SV CHD. In our propensity score-matched cohorts, all outcome estimates at 4 time points during the first year of life were better in the HM/breastfeeding 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 2 decades of research in preterm populations, and are important in light of a 2022 review by Burge et al[44] 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,[45] prophylactic antibiotics, and delayed enteral feeding are known to play a role in NEC and intestinal injury in neonates.[44]

Despite potential differences in cause 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[16,24–26] 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.[20,21,46] Our results align with the well-designed retrospective cohort study by Cognata et al,[20] 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,[20] with the same population, Kataria-Hale et al[46] found no difference in postoperative

Table 5. Average Treatment Effect Among the Treated of High-Interstage-HM Feeding or DBF Duration (S1P Discharge to S2P) for Key Outcomes in Propensity Score-Matched Cohorts

Variable	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			
No. of unplanned interstage readmissions	0.97[*]	(0.72–1.30)	0.835
Any interstage readmission for adverse events[‡]	0.89[†]	(0.52–1.54)	0.684
Infection-related interstage readmission[§]	0.86[†]	(0.30–2.45)	0.684
Feeding-related interstage readmission[‖]	0.66[†]	(0.30–1.47)	0.310
All-cause mortality[#]	0.31[†]	(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			
No. of unplanned interstage readmissions	0.89[*]	(0.61–1.30)	0.531
Any interstage readmission for adverse events[‡]	0.97[†]	(0.54–1.74)	0.911
Infection-related interstage readmission[§]	0.97[†]	(0.32–2.98)	0.959
Feeding-related interstage readmission[‖]	0.46[†]	(0.20–1.06)	0.069
All-cause mortality[#]	0.00[†]	NC[**]	<0.001[††]

DBF indicates direct breastfeeding; HM, human milk; NC, not computable; OR, odds ratio; RR, rate ratio; S1P, stage 1 palliation; and S2P, stage 2 palliation.

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

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

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

[§] Includes pneumonia, sepsis, wound infection/dehiscence, and infection requiring intravenous antibiotics.

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

[#] Between S2P and 1 year of age.

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

[††] $P < 0.05$

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, because infants with high-HM feeding during the S1P hospitalization had 72% lower odds of postoperative NEC. This result is particularly intriguing, because the literature on 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 versus 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. Although the 2022 randomized controlled trial conducted by Blanco et al[21] 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 United States, and the study was not powered for the NEC outcome. Exposure to a bovine milk-based fortifier/formula, which has been shown to increase the risk of NEC,[47] is the current standard of care.[12] 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,[48,49] exosomes,[50] fatty acids and lipids,[51] lactoferrin,[52] immunoglobulins,[52,53] and many other bioactive factors[54] offering tailored protection against NEC and other hospital-associated diseases. Emerging evidence reveals that HM from the infant's own lactating parent (ie, maternal HM) is associated with epigenetic variation in DNA methylation,[55,56] 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.[57] Studies have characterized the gastrointestinal microbiome[58] of preterm populations, revealing frequent dysbiosis driven by exposure to infant formula, antibiotics, and delivery mode (ie, cesarean section) that could contribute to NEC.[59] Interestingly,

Table 6. Average Treatment Effect Among the Treated of HM Feeding and DBF at S2P for Key Outcomes in Propensity Score-Matched Cohorts

Variable	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[‡]	0.94[*]	(0.53–1.68)	0.838
S2P postop sepsis	0.61[*]	(0.28–1.30)	0.196
S2P postop hospital LOS	0.82[†]	(0.69–0.97)	0.018[‖]
All-cause mortality[§]	0.85[*]	(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[*]	(0.16–1.92)	0.353
S2P postop sepsis	0.49[*]	(0.12–1.98)	0.315
S2P postop hospital LOS	0.75[†]	(0.57–0.99)	0.040[‖]
All-cause mortality[§]	0.49[*]	(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[‖]	0.39[*]	(0.11–1.34)	0.136
S2P postop sepsis	0.87[*]	(0.18–4.12)	0.861
S2P hospital LOS	0.71[†]	(0.57–0.89)	0.003[‖]
All-cause mortality[§]	0.24[*]	(0.03–1.88)	0.174

DBF indicates direct breastfeeding; HM, human milk; LOS, length of stay; postop, postoperative; OR, odds ratio; RR, rate ratio; and S2P, stage 2 palliation.

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

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

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

[§] Between S2P and 1 year of age.

[‖] $P < 0.05$.

two 2022 randomized controlled trials[60,61] examining infant fortifiers highlight the crucial role of maternal HM in positively shaping the preterm gastrointestinal microbiome, with Kumbhare et al[60] identifying volume of maternal HM 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,[62–67] and there has been no investigation into HM composition in the context of CHD. A 2022 study by Huang et al[62] provided 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,[58] with consequent inflammatory and immune imbalances potentially contributing to poor clinical outcomes, including NEC. Huang and colleagues note the key role of HM/breastfeeding (eg, HM oligosaccharides) in establishing normal gut *Bifidobacterium* colonization and reducing pathogenic activity, and speculate that low-HM/breastfeeding prevalence could contribute to gut dysbiosis in the context of CHD.[62] 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,[67] studies,[63,65,66] or reviews[64] identified on the topic of the gut microbiome in patients with CHD, only 1 briefly mentions HM/breastfeeding,[66] and none discuss HM/breastfeeding as a therapeutic intervention for gut dysbiosis.

The omission of HM/breastfeeding from the CHD gut microbiome literature is not entirely surprising, because support for HM/breastfeeding in the CHD population has been historically inadequate and underprioritized by the health care team,[14,68–71] contributing to low prevalence of these feeding practices.[12] We also speculate that, because 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 the novel research by Huang et al[62] 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,[71] a process with clear analogies to the SV CHD clinical course. 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, whereas those with high-direct-breastfeeding duration had 100% lower odds of postoperative sepsis. No infants in the interstage high-breastfeeding group were readmitted for sepsis, although the overall prevalence of interstage sepsis was low. HM has been associated with lower rates of sepsis[16,17,19,30,72,73] 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[74]). A 2023 study by Ghosh et al[75] reported a 2.58-fold 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 with 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 versus 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 that 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 breastfeeding and infection or sepsis in any hospitalized neonates.

Our finding of reduced odds of sepsis in high-breastfeeding groups offers novel evidence that direct breastfeeding as a mode of HM delivery may be particularly beneficial in preventing sepsis in infants with SV CHD. Interestingly, a 2019 study[76] using a robust, multimethod 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 with 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.[76–79] This microbial communication between infant and parent during breastfeeding could be 1 mechanism to explain the changes in the immunological composition of HM in response to pathogenic organisms that can lead to sepsis,[80] and suggests that direct breastfeeding 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 breastfeeding 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 <1 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-breastfeeding duration had a 23% lower mean S1P length of stay. Associations between HM and shorter length of stay have been demonstrated for preterm infants[25,81] and infants with other surgical anomalies,[18,30,73,82] although results are inconsistent, may be dose dependent,[18,30,82] and may differ between maternal HM[81] and donor HM.[25] To our knowledge, only 1 study has examined associations between HM and length of stay for infants with CHD. Yu et al[83] found that infants fed HM had a 3.9-days shorter mean length of stay compared with a formula-feeding group in a cohort with varied CHD diagnoses; however, this study exhibited a high risk of bias.[15]

We did not identify any studies examining direct breastfeeding 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[84] reported an association between direct breastfeeding as the first mode of oral feeding (compared with bottle) for preterm infants and ≈1-week earlier neonatal intensive care unit discharge. Our study is unique in that it addresses the critical gap in knowledge about direct breastfeeding in this population and suggests some differential benefits.

Establishing causality between HM or breastfeeding and S1P length of stay in this population is challenging. Hospital length of stay has often been considered as a predictor of HM/breastfeeding practices rather than as an outcome impacted by infant feeding,[85] and the psychological stress of extended hospitalization, postoperative complications, or family/work obligations could impact a parent's ability to provide HM/breastfeeding. These are potentially unmeasured confounders that could impact our results, and there is likely some multidirectionality between HM/breastfeeding 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.[86] 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 S1) (eg, preoperative instability, intubation duration, major postoperative procedures) and parental access to supportive resources (eg, insurance type, social deprivation index score of the infant's residential zip code, 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 breastfeeding and length of stay remained strong. As a partial explanation, we hypothesize a causal pathway between HM/breastfeeding; reduced incidence of NEC, infection, and sepsis; and S1P hospital length of stay.[29]

The potential for a causal effect of HM and/or breastfeeding on length of stay is further supported by the results from the S2P hospitalization, in which the temporal relationship between HM/breastfeeding and S2P postoperative length of stay was more clearly defined. Once again, length of stay was significantly shorter in all HM/breastfeeding 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[87] of practices that impact both HM/breastfeeding 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,[88] our findings suggest that improving HM/breastfeeding prevalence has the potential to not only improve the health of infants with SV CHD but also to reduce economic costs for families, payers, and institutions.

Mortality

Although most analyses of all-cause mortality did not reach statistical significance in this study, all estimates were substantially lower in the HM and breastfeeding groups. The clinical importance was particularly striking for direct-breastfeeding groups, with estimates of 75% to 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/breastfeeding practices for infants with SV CHD. In regard to direct breastfeeding, it may be tempting to assume that infants who are able to breastfeed 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 breastfeeding in the context of severe CHD presentation.[14] We speculate that the achievement of the complex neurodevelopmental skill of direct breastfeeding 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. Although registry data in this rare disease population offer advantages, we could not fully characterize an infant's HM/breastfeeding 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 maternal HM and donor HM are not equivalent, because many of the protective bioactive components of maternal HM are eliminated during pasteurization, and the nutritional composition and microbiota differ.[89] 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. Additionally, although we had a low proportion of unmatched infants in our exposed cohorts (see Table S1), it is possible that the results may not be generalizable to all infants with SV CHD.

Considering the known association between HM/breastfeeding and maternal factors such as race and/or economic status, our inclusion of variables derived from an infant's zip code is 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/breastfeeding or factors such as previous breastfeeding 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/breastfeeding throughout the infant's first year of life should also include detailed analysis of relevant family, maternal, and social factors.

CONCLUSIONS

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-breastfeeding 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/breastfeeding 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 breastfeeding for infants with SV CHD. Our findings demonstrate that increasing the dose and duration of HM and direct breastfeeding has strong potential to substantially improve the health outcomes of these vulnerable infants.

ARTICLE INFORMATION

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Disclosures

D.L.S. is an advisory board member for Medela Americas and has received speaker honoraria including speakers bureau, symposia, and expert witness. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S5
Figures S1–S3

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