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Risk factors for early occurrence of malnutrition in infants with severe congenital heart disease

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Abstract

Purpose: To identify the risk factors of early occurrence of malnutrition in infants with severe congenital heart disease (CHD) during their first year of life.

Methods and Results: Retrospective longitudinal multicentre study carried out from January 2014 to December 2020 in two tertiary care CHD centres. Four CHD hemodynamic groups were identified. Malnutrition was defined by a Waterlow score under 80% and/or the need for calorie-enriched formula. A total of 216 infants with a severe CHD, *e.g.*, requiring cardiac surgery, cardiac catheterization, or hospitalization for heart failure during their first year of life were included in the study. Malnutrition was observed among 43% of the cohort, with the highest prevalence in infants with increased pulmonary blood flow (71%) compared to the others hemodynamic groups ($p < 0.001$). In multivariate analysis, low birthweight (OR 0.62, 95% CI 0.44-0.89, $p = 0.009$), CHD with increased pulmonary blood flow (OR 4.80, 95% CI 1.42-16.20, $p = 0.08$), heart failure (OR 9.26, 95% CI 4.04-21.25, $p < 0.001$), and the number of hospitalizations (OR 1.35, 95% CI 1.08-1.69, $p = 0.009$) during the first year of life were associated with malnutrition (AUC 0.85, 95% CI 0.79-0.90).

Conclusion: In infants with a severe CHD, early occurrence of malnutrition during the first year of life affected a high proportion of subjects. CHD with increased pulmonary blood flow, low birthweight, heart failure, and repeated hospitalizations were risk factors for malnutrition. Further studies are required to identify optimal nutritional support in this population.

What Is Known

- Malnutrition is a known morbidity and mortality factor in children with severe congenital heart disease.

What is new:

- Early occurrence of malnutrition during the first year of life in infant severe congenital heart disease (CHD) was high (43%).
- CHD with increased pulmonary blood flow, low birthweight, heart failure, and repeated hospitalizations during the first year of life were risk factors for malnutrition.
- These results suggest the need for further studies to identify optimal nutritional support in this population.

Introduction

Congenital heart disease (CHD) is the leading cause of congenital anomalies, representing a major global health problem which affects 8 in 1,000 live births[1, 2]. Thirty percent of these patients require cardiac surgery, cardiac catheterization, or hospitalization for heart failure in their first year of life[3].

Cardiac and extracardiac factors create an imbalance [4] between increased metabolic demands, due to heart failure and increased work of breathing, and inadequate nutritional intakes, in relation notably with altered gastrointestinal perfusion and delayed oromotor skill attainment associated with the frequent genetic syndromes of these patients[5, 6]. This results in deficits of energy, protein, or micronutrients, that may negatively affect the infant's growth and development[7].

Prior studies in the population of infants with CHD have shown that malnutrition was associated with increased infection risk and inflammatory response, poor wound healing, longer intensive care unit (ICU) and total hospital stay. Ultimately, it results in poorer neurodevelopmental outcomes, and decreased survival after cardiac surgery [8]. Therefore, nutritional optimization provides a unique opportunity to improve survival, development, and quality of life in patients with severe CHD[9]. In general, infants with CHD have a normal weight for gestational age at birth, but nutrition and growth problems arise before the age of 6 months, affecting nearly 60% of them[10, 11]. CHD is a heterogeneous group of diseases with various pathophysiology and complications, and nutritional risks are probably not identical in all patients. Nevertheless, this has been scarcely reported in the literature.

Prospective studies have highlighted the positive impact of a pre- and post-operative nutritional interventions in CHD, in terms of reduction of hospital length of stay [12] and infection [13]. We may hypothesize that an early screening of malnutrition, during the first year of life, could allow early a nutritional intervention, and reduce the risks of morbidity and mortality due to poor nutritional status, especially in infants with severe CHD [14, 15].

This study aimed to assess the factors associated with early occurrence of malnutrition in infants with severe congenital heart disease (CHD) during their first year of life, in order to identify the population at risk who could benefit from an early nutrition program and thus reduce the occurrence of malnutrition

Methods

Study design

This retrospective longitudinal bicentric study was carried out in two tertiary care paediatric and congenital cardiology centers in France: Montpellier University Hospital and Saint-Pierre Institute.

Patient population

Infants from birth to one year old with a CHD, according to the anatomical and clinical classification (ACC-CHD classification), were screened from our hospital-based database, over a retrospective period of 7 years. The ACC-CHD classification uses a nomenclature based on the International Paediatric and

Congenital Cardiac Code (IPCC code), defining all CHD lesions into 10 categories and 23 subcategories [16]. The patient follow-up was defined between birth and the age of one.

The cases with a severe CHD were identified, defined as the occurrence of at least one of the following clinical events during the first year of life [3]: hospitalization for heart failure (hepatomegaly, tachycardia, tachypnea, feeding difficulties), surgical cardiac intervention, or interventional cardiac catheterization. Patients were not included in case of absent or erratic follow-up, and/or in palliative care.

To define the CHD hemodynamic characteristics, we used a pathophysiological classification based upon the clinical consequence of structural defects on the physiology of blood circulation [17], with four hemodynamic groups: group 1, CHD with increased pulmonary blood flow (septal defects without pulmonary obstruction and left-to-right shunt); group 2, CHD with decreased pulmonary flow (septal defects with pulmonary obstruction and right-to-left shunt); group 3, CHD with obstruction to blood progression and no septal defects (no shunt); group 4, CHD so severe as to be incompatible with postnatal blood circulation. The group 5, corresponding to silent CHD until adult age, was not used this study.

To define malnutrition, we used the French reference anthropometric values [18]. The early occurrence of malnutrition during the first year of life, *e.g.*, the study primary outcome, was defined as follows: (i) wasting, with a Waterlow score < 80%; this score is the ratio of the measured weight to the expected weight for height [19], and/or (ii) underweight, with a weight-for-age value <-2 standard deviations (SD) [18], prompting the physician of the paediatric and congenital cardiology department to prescribe calorie-enriched formula.

Nutrition data also collected to assess issues related to food intake notably digestive symptoms and details on nutritional support.

Outcomes

The primary outcome was the early occurrence of malnutrition during the first year of life in infants with severe CHD.

Statistics

We made the hypothesis of an increased incidence of malnutrition in the CHD group 1 compared to the 3 other groups. Based on malnutrition incidence ratio of 60% in the CHD group 1, versus 40% in the CHD groups 2–4 [11], 65 patients in the group 1 and 65 in the groups 2–4 were necessary to demonstrate a significant difference with a power of 90% and 2-sided $p < 0.05$. According to the number of new patients with a severe CHD followed each year in the participating centres, and taking into consideration that the group 1 represents approximately 30% of these patients, a retrospective data collection over a period of 7 years was necessary to satisfy the sample size calculation.

The study population was described with means and standard deviations (SD) for quantitative variables, and with numbers and percentages for qualitative ones. The continuous variables distributions were

tested using the Shapiro-Wilk test. Quantitative variables were compared using the Student's t-test when the distribution was Gaussian and with the Mann-Whitney test, otherwise. For qualitative variables, groups were compared using the chi-squared test or Fisher's exact test. P values were corrected by the False Discovery Rate method for pairwise comparisons of pathophysiological classification of the CHD.

In order to analyze the association between the degree of increased pulmonary blood flow (group 1) and the early occurrence of malnutrition, we selected the most frequent CHD reflecting this condition, e.g., the ventricular septal defect (VSD). A receiver operating characteristic (ROC) curve analysis was used to estimate the area under the curve (AUC) with 95% CI and to establish the cut-off of VSD size optimizing the Youden index.

To identify the factors associated with early occurrence of malnutrition, a multiple logistic regression was used. All clinically relevant variables with a p-value ≤ 0.20 in univariate analysis were included in the model. The final model was determined using a backward selection with a α -to-stay set at 0.10.

The statistical significance was set at 0.05 and analyses were performed using software SAS Enterprise Guide, version 7.13 (SAS Institute, Cary, NC, USA).

Results

Population

From January 2014 to December 2020, 746 infants were hospitalized for CHD. Severe CHD affected 249 infants (33%). Thirty-three patients (13%) were excluded, according to the exclusion criteria. A total of 216 infants were included in the study. No parents or legal guardians refused to participate in the study (Fig. 1). The study population included 18% of premature infants, born before 37 weeks' gestation. Intrauterine growth restriction (IUGR), defined as a birthweight <-2 SD, was present in 13%. Patients' perinatal characteristics are summarized in Table 1.

Table 1
Perinatal characteristics according to the pathophysiological classification of the CHDs.

Variables	all	Group 1	Group 2	Group 3	Group 4	Pvalue	Significant difference *
N	216	76	41	23	76		
Sex ratio (male/female)	1.18	0.69	1.56	1.09	1.81	0.02	G1 < G4
Gestational age, weeks	37.9 ± 3.0	37.4 ± 4.0	37.8 ± 2.4	37.3 ± 3.0	38.6 ± 1.8	0.11	-
Birth weight, g	2926 ± 696	2776 ± 817	2959 ± 663	2750 ± 552	3108 ± 581	0.01	G4 > G1,G3
Birth weight (SD)	-0.41 ± 1.10	-0.43 ± 1.24	-0.35 ± 0.75	-0.59 ± 1.32	-0.36 ± 0.92	0.81	-
Birth height, cm	47.9 ± 4.3	46.9 ± 5.1	48.2 ± 4.0	47.6 ± 3.4	48.7 ± 3.8	0.04	G1 < G4
Birth height (SD)	-0.33 ± 1.14	-0.45 ± 1.25	-0.25 ± 1.03	-0.33 ± 1.32	-0.26 ± 1.06	0.71	-
Birth head circumference, cm	33.4 ± 2.9	32.7 ± 3.4	33.3 ± 2.3	32.7 ± 2.1	34.2 ± 2.6	0.02	G4 > G1,G3
Birth head circumference (SD)	-0.22 ± 1.03	-0.18 ± 1.21	-0.29 ± 0.88	-0.60 ± 1.19	-0.10 ± 0.86	0.23	-
Genetic syndrome, N (%)	31 (14)	20 (26)	5 (12)	3 (13)	3 (4)	< 0.01	G1 > G4
Down syndrome, n (% n/N)	15 (48)	11 (55)	2 (40)	2 (67)	0 (0)	0.40	-
Di George syndrome, n (% n/N)	8 (26)	4 (20)	2 (40)	1 (33)	1 (33)	0.65	-
Others, n (% n/N)	8 (26)	5 (25)	1 (20)	0 (0)	2 (67)	1.00	-
Values are numbers (%) or means ± SD.							
Abbreviations: CHD, congenital heart disease; SD, standard deviation.							
* False Discovery Rate method were applied for pairwise comparisons							

Cardiological data

The distribution of infants in terms of CHD hemodynamic group was 76 (35%) in group 1, 41 (19%) in group 2, 23 (11%) in group 3, and 76 (35%) in group 4 (Table 2). The types of CHD anatomy according to the ACC-CHD classification is reported in Supplementary Table 1. The most represented groups were the

group 8.2 (27% of patients), which includes notably tetralogy of Fallot and pulmonary atresia, the group 9 (19% of patients), which includes aortic coarctation and patent ductus, and the group 7 (17% of patients), which includes ventricular septal defect.

Table 2

Cardiological management and evolution according to the pathophysiological classification of CHDs.

Characteristics	all	Group 1	Group 2	Group 3	Group 4	Pvalue	Significant difference *
N	216	76	41	23	76		
Heart failure in the first year, n (%)	93 (43)	64 (84)	8 (20)	5 (22)	16 (21)	< 0.01	G1 > G2,G3,G4
Cardiological treatment, n (%)	190 (88)	71 (93)	38 (93)	14 (61)	67 (88)	< 0.01	G3 < G1,G2,G4
Diuretics, n (%)	174 (81)	70 (92)	35 (85)	10 (43)	59 (78)	< 0.01	G3 < G1, G2, G4 ; G4 < G1
ACE inhibitors, n (%)	104 (48)	50 (66)	16 (39)	5 (22)	33 (43)	< 0.01	G1 > G2,G3,G4
Heart surgery in the first year, n (%)	173 (80)	53 (70)	40 (98)	5 (22)	75 (99)	< 0.01	G3 < G1 < G2,G4
Age at first surgery, months	3.4 ± 3.5	4.9 ± 2.8	6.5 ± 2.7	2.8 ± 4.4	0.7 ± 1.8	< 0.01	G4 < G1 < G2
Surgical complication, n (% n/N)	28 (16)	7 (13)	3 (8)	0 (0)	18 (24)	0.10	-
Heart catheterization in the first year, n (%)	72 (33)	11 (14)	2 (5)	20 (87)	39 (51)	< 0.01	G3 > G4 > G1,G2
Age at first heart catheterization, months	2.3 ± 3.5	6.6 ± 3.3	5.5 ± 7.8	1.7 ± 3.1	1.3 ± 2.6	< 0.01	G1 > G3,G4
Number of hospitalizations, n (%)	2.7 ± 1.8	2.9 ± 1.8	3.8 ± 2.2	2.0 ± 1.4	2.2 ± 1.2	< 0.01	G2 > G1 > G3,G4
Total length of stay, days	45 ± 48	55 ± 62	36 ± 29	31 ± 32	44 ± 44	0.12	-
Death in the first year of life, n (%)	5 (2)	1 (1)	0 (0)	1 (4)	3 (4)	0.43	-
Values are numbers (%) or means ± SD.							
Abbreviations: ACE, Angiotensin-converting enzyme; CHD, congenital heart disease; ICU, intensive care unit; SD, standard deviation.							
* False Discovery Rate method were applied for pairwise comparisons							

The distribution of heart failure occurrence during the first year of life was different between the 4 groups ($p < 0.01$), the highest percentage being in the group 1 (84%). Cardiac surgery was required for 80% of infants, overall, and for almost all infants in groups 2 and 4. Mean age at surgery was lower in patients of the group 4, who generally underwent surgery during the first month of life. Surgical complications were observed in 16% of operated children with infectious, ENT, pulmonary, rhythmic, or thrombotic complications. Cardiac catheterization procedures were more frequent in the group 3. Children spent 45 ± 48 days in hospitalization during their first year of life, overall, and 55 ± 62 days for children in the group 1. Among the 216 infants included in the study, five died during the one-year follow-up, of which 3 from the group 4.

Nutrition data

The occurrence and the description of gastrointestinal symptoms according to the CHD hemodynamic group are reported in Table 3. During the one-year follow-up, enteral nutrition for more than 7 days was provided in 24 (11%) infants, including nasogastric tube in 21 subjects and gastrostomy in 3 subjects.

Table 3

Gastrointestinal symptoms and nutritional management according to pathophysiological classification of CHDs.

Characteristics	all	Group 1	Group 2	Group 3	Group 4	Pvalue	Significant difference *
N	216	76	41	23	76		
Digestive symptoms, n (%)	56 (26)	33 (43)	9 (22)	4 (17)	10 (13)	< 0.01	G1 > G2,G3,G4
Feeding disorder, n (% n/N)	14 (25)	10 (30)	1 (11)	1 (25)	2 (20)	0.79	-
Gastroesophageal reflux & vomiting, n (% n/N)	34 (61)	20 (61)	5 (56)	4 (100)	5 (50)	0.42	-
NEC & digestive perfusion disorder, n (% n/N)	12 (21)	6 (18)	3 (33)	0 (0)	3 (30)	0.52	-
Cow's milk protein intolerance, n (% n/N)	12 (21)	3 (9)	3 (33)	2 (50)	4 (40)	0.03	NS
Enteral nutrition n (%)	24 (11)	17 (22)	1 (2)	1 (4)	5 (7)	0.51	-
Nasogastric tube n (% n/N)	21 (88)	14 (82)	1 (100)	1 (100)	5 (100)	1.00	-
Gastrostomy n (% n/N)	3 (12)	3 (18)	0 (0)	0 (0)	0 (0)		
Required calorie-enriched formula	78 (36)	49 (64)	8 (20)	4 (17)	17 (22)	< 0.01	G1 > G2, G3, G4
Malnutrition, n (%)	93 (43)	54 (71)	10 (24)	6 (26)	23 (30)	< 0.01	G1 > G2,G3,G4
Values are numbers (%) or means \pm SD.							
Abbreviations: CHD, congenital heart disease; NEC, necrotizing enterocolitis.							
* False Discovery Rate method were applied for pairwise comparisons							

Table 4
Factors associated with malnutrition in multivariate analysis

Factors		Odds Ratio [95% CI]	Pvalue
Birth weight (SD)		0.62 [0.44;0.89]	0.01
Pathophysiological classification			0.08
	Group 1 vs Group 2	4.80 [1.42;16.20]	
	Group 3 vs Group 2	2.11 [0.46;9.69]	
	Group 4 vs Group 2	3.00 [0.95;9.47]	
Heart failure in the first year	Yes vs No	9.26 [4.04;21.25]	< 0.001
Number of hospitalizations		1.35 [1.08;1.69]	0.01
Abbreviation: SD, standard deviation.			

Malnutrition occurred in 93 (43%) infants. Among them, 65 (70%) had a Waterlow score < 80%, and 78 (84%) required calorie-enriched formula. Enrichment involved mainly the prescription of an isocaloric formula (70/78, 90%), sometimes associated with glucose polymer (17/78, 22%), lipid concentrated formula (13/78, 17%) or protein concentrated formula (4/78, 5%).

Malnutrition and gastrointestinal symptoms occurred differently between CHD severity groups ($p < 0.01$), in particular they were more frequent in the group 1 than in groups 2–4.

Factors associated with malnutrition

Factors associated with malnutrition in univariate analyses are summarized in Fig. 2.

In multivariate analysis, factors associated with malnutrition were birthweight SD score, CHD with increased pulmonary blood flow (group 1), heart failure, and the number of hospitalizations during the first year of life. The area under the curve (AUC) of the model was 0.85 (95% CI 0.79–0.90).

Subgroup analysis in infants with VSD found that a cut-off value of VSD size ≥ 5 mm had a sensitivity of 74%, specificity of 73%, positive predictive value of 90% and negative predictive value of 47% (AUC 0.71, 95% CI 0.55–0.88) for the early occurrence of malnutrition.

Discussion

In this cohort of 216 infants with a severe CHD, early occurrence of malnutrition during the first year of life affected a high proportion of 43% of patients. Statistical modelling individualized several risk factors for malnutrition, including birthweight, CHD hemodynamic group, heart failure, and the number of hospitalizations during the first year of life.

The early occurrence of malnutrition during the first year of life in infants with a severe CHD was affected by the hemodynamic presentation of the cardiac malformation. Indeed, infants in with a CHD characterized by an increased pulmonary blood flow (group 1) were significantly more at risk, with malnutrition rates reaching 71% compared to an average of 43% in the cohort. Such conditions correspond to left-to-right shunts without any pulmonary protection (ventricular septal defect, atrio-ventricular septal defect, ductus arteriosus, truncus arteriosus, etc.), and commonly marked by an early onset of infant heart failure and a high level of energy expenditure [20, 21]. These results are consistent with the data from Cameron and al. published in 1995, who reported 33% of acute malnutrition in children (of all ages) hospitalized for CHD, and a rate of 60% of malnutrition (acute and chronic) in children with left-to-right shunt [11]. Classically, infants with increased pulmonary blood flow related to significant left-to-right shunt cannot satisfy the increase in energy needs. In our study, a very large majority of infants in this hemodynamic group presented with a severe heart failure requiring hospitalization. Significant left-to-right shunt results in poor systemic perfusion, decreased blood flow available for the gastrointestinal tract, and, ultimately, impaired nutrient absorption [9]. In addition, dyspnoea and gastrointestinal dysmotility generate feeding disorders and gastro-oesophageal reflux, which are also associated with malnutrition [22–24].

Interestingly, infants of the other hemodynamic groups were less affected by malnutrition in this study, despite the CHD severity. In particular, CHD with decreased pulmonary flow (group 2), mostly represented by Tetralogy of Fallot, underwent corrective cardiac surgery before the age of six months, preventing any long-term effects of chronic cyanosis, as opposed to reports from historical cohorts [25]. Similarly, CHD with obstruction to blood progression and no septal defects (group 3), mostly represented by pulmonary valve stenosis, also benefited from early cardiac repair by intervention catheterization. As a result, symptoms including notably heart failure were much less frequent in patients of hemodynamic groups 2, 3. For CHD incompatible with postnatal blood circulation (group 4), palliative or definitive cardiac surgical repair was performed immediately after birth, limiting the occurrence of prolonged heart failure. In hypoplastic left heart syndrome, *e.g.*, the most severe and complex CHD, active nutritional intervention has been integrated into the Norwood surgical program to improve the overall prognosis [26, 27].

In this study, the early occurrence of malnutrition during the first year of life in infants with a severe CHD was significantly higher, in the multivariate analysis, in subjects with low birthweight and repeated hospitalizations. New-borns with IUGR received a specific nutritional support during the hospital stay, but it is uncertain whether dietary monitoring extended beyond hospitalization. In addition, some conditions of IUGR were underpinned by genetic syndromes that inherently involve lower weight growth, or even malnutrition. Prolonged hospitalization is commonly associated with a high risk of undernutrition [28], but this association is not purely causal as the occurrence of malnutrition in severe chronic paediatric conditions remains multifactorial. Nevertheless, the association between hospitalization and malnutrition in infant CHD remains important to consider, as prolonged hospital length of stay is associated with worse neurodevelopmental outcome [29, 30].

This study highlighted the absence of a uniform nutritional protocol with patients receiving various forms of calorie-enriched formula (isocaloric milk, lipid and/or glucose and/or protein enriched food), a different time for introduction of enrichment, and a lack of individualized prescription of the enrichment adapted to the child and the cardiac condition. To this end, Tsintoni et al. proposed that children with CHD should receive, at the level of the institution, clear individual guidelines regarding initiation of enteral feeding, estimation of their caloric needs, and adequate nutritional intake [31]. In the literature, specific nutritional care has been described for the Norwood surgical program in hypoplastic left heart syndrome, a severe CHD representing less than 2% of CHD [32]. Similarly, pre- and post-operative nutritional interventions have also been described for complex CHD [12]. Therefore, the evaluation of an early personalized nutritional intervention by a randomized controlled trial involving the overall spectrum of infant CHD, would be of great interest.

Study limitation

This study was a retrospective chart review conducted via the electronic medical record. There are limitations inherent to this type of study, particularly the variability in age at which the growth parameters were measured. As this information was systematically informed in the medical record, we defined malnutrition on 2 criteria, wasting and underweight, resulting in prescription of calorie-enriched formula by the physician. Nevertheless, this prescription may be determined by the physician' awareness of the importance of nutritional management. Unfortunately, the mid-arm over head circumference ratio, an interesting parameter to assess nutritional status in infants [33], was barely informed in the medical record.

Conclusion

In infants with a severe CHD, early occurrence of malnutrition during the first year of life affected a high proportion of 43% of subjects and was more marked in hemodynamic groups involving increase pulmonary blood flow. In multivariate analysis, risk factors for malnutrition included birthweight, CHD hemodynamic group, heart failure, and repeated hospitalizations during the first year of life. Future studies are required to assess whether early nutritional intervention may improve the nutritional status and decrease malnutrition-associated morbidities in this high-risk population.

Declarations

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Dr Mignot, Ms Huguet, Pr Cambonie, Dr Kollen and Dr Gavotto. The first draft of the manuscript was written by Dr Mignot, Pr Cambonie, Dr Kollen and Dr Gavotto and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

The study was conducted in compliance with the Good Clinical Practices and Declaration of Helsinki principles. The Institutional Review Board of Montpellier University Hospital (IRB-MPT_2020_02_202000362) gave its approval and all parents or legal guardians gave their informed consent.

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Figures

Infants in electronic medical
record with code for CHD
between 01/01/2014 and
31/12/2019
(n=746)

497 excluded
-Did not fulfill inclusion criteria

Infants with severe CHD
(n= 249)

33 excluded
- Palliative medical support only (n=3)
- Absence of follow-up (n= 16)
- Erratic follow-up and excessive missing data (n= 14)

Infants included in analysis
(n= 216)

Figure 1

Flowchart

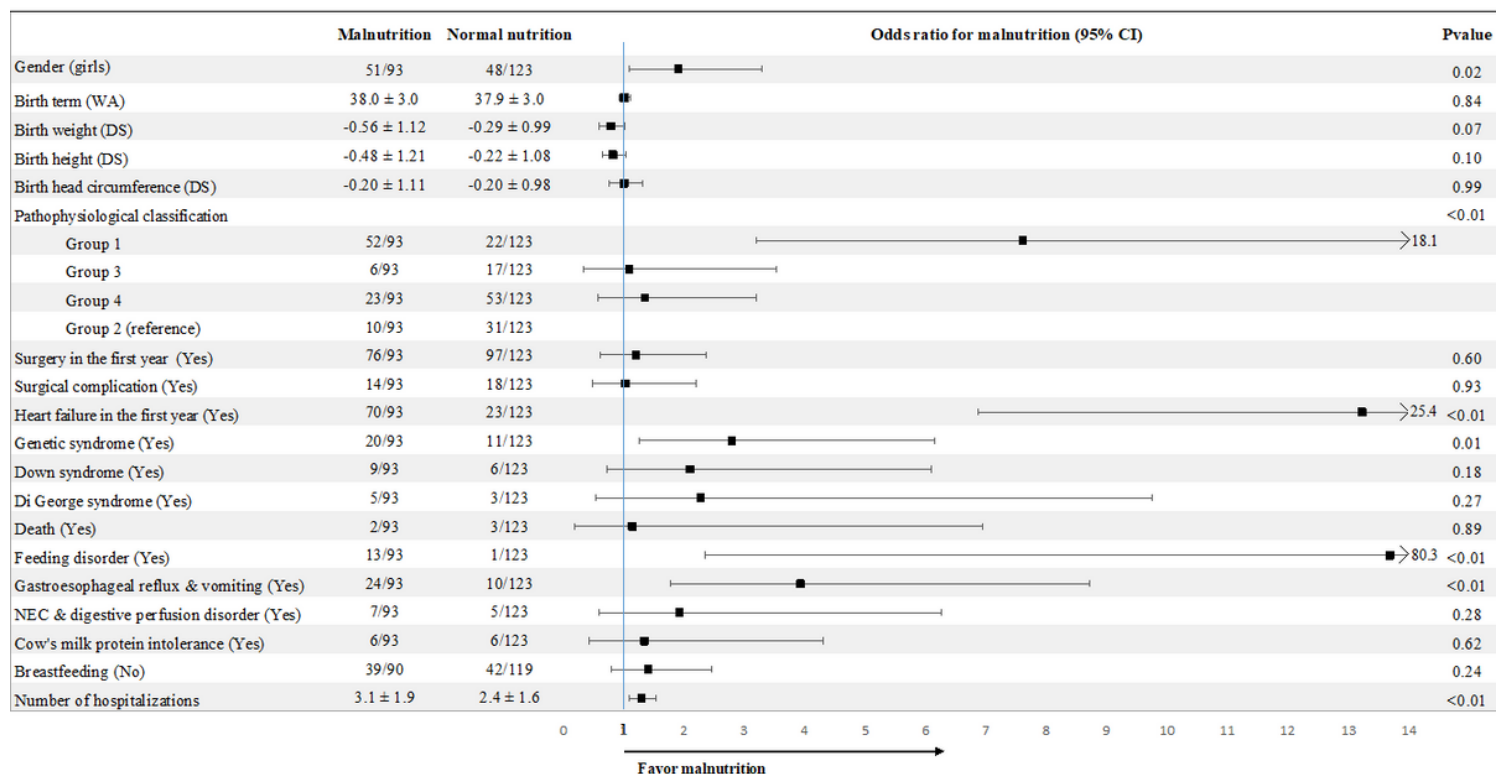


Figure 2

Factors associated with malnutrition in univariate analyses.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTable1.docx](#)