Pediatric Cardiology (2021) 42:543–553
https://doi.org/10.1007/s00246-020-02512-x

ORIGINAL ARTICLE

Medical Interventions for Chylothorax and their Impacts on Need for Surgical Intervention and Admission Characteristics: A Multicenter, Retrospective Insight

Rohit S. Loomba[1,2] · Joshua Wong[2] · Megan Davis[2] · Sarah Kane[2] · Brian Heenan[2] · Juan S. Farias[3] · Enrique G. Villarreal[3] · Saul Flores[4]

Received: 15 September 2020 / Accepted: 17 November 2020 / Published online: 4 January 2021

Abstract

The incidence of chylothorax is reported from 1–9% in pediatric patients undergoing congenital heart surgery. Effective evidenced-based practice is limited for the management of post-operative chylothorax in the pediatric cardiac intensive care unit. The study characterizes the population of pediatric patients with cardiac surgery and chylothorax who eventually require pleurodesis and/or thoracic duct ligation; it also establishes objective data on the impact of various medical interventions. Data were obtained from the Pediatric Health Information System database from 2004–2015. Inclusion criteria for admissions for this study were pediatric admissions, cardiac diagnosis, cardiac surgery, and chylothorax. These data were then divided into two groups: those that did and did not require surgical intervention for chylothorax. Other data points obtained included congenital heart malformation, age, gender, length of stay, billed charges, and inpatient mortality. A total of 3503 pediatric admissions with cardiac surgery and subsequent chylothorax were included. Of these, 236 (9.4%) required surgical intervention for the chylothorax. The following cardiac diagnoses, cardiac surgeries, and comorbidities were associated with increased odds of surgical intervention: d-transposition, arterial switch, mitral valvuloplasty, acute kidney injury, need for dialysis, cardiac arrest, and extracorporeal membrane oxygenation. Statistically significant medical interventions which did have an impact were specific steroids (hydrocortisone, dexamethasone, methylprednisolone) and specific diuretics (furosemide). These were significantly associated with decreased length of stay and costs. Dexamethasone, methylprednisolone, and furosemide were associated with decreased odds for surgical intervention. These analyses offer objective data regarding the effects of interventions for chylothorax in pediatric cardiac surgery admissions. Results from this study seem to indicate that most post-operative chylothoraxes should improve with furosemide, a low-fat diet, and steroids.

Keywords Chylothorax · Cardiac surgical procedure · Pediatrics · Congenital heart defects · Mortality · Length of stay

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00246-020-02512-x) contains supplementary material, which is available to authorized users.

✉ Enrique G. Villarreal
quique_villarreal93@hotmail.com

1 Department of Pediatrics, Chicago Medical School, Chicago, IL, USA

2 Division of Cardiology, Advocate Children's Hospital, Chicago, IL, USA

3 Tecnologico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Monterrey, Nuevo Leon, Mexico

4 Section of Critical Care, Texas Children's Hospital, Houston, TX, USA

Introduction

Chylothorax is present in 1%–9% of pediatric cardiac surgery admissions and can greatly increase resource utilization along with morbidity and mortality [1–3]. There is a paucity of data on how to manage post-operative chylothorax, and current protocols are often based on anecdotal evidence or evidence from case reports or small studies [4, 5].

The purpose of these analyses was to use a large pediatric administrative database to (a) compare pediatric cardiac surgery admissions with chylothorax that did and did not require surgical intervention for chylothorax; (b) determine the impact of various medical interventions for chylothorax on various admission characteristics.

Methods

As this study utilized de-identified data from a national database, no consents were obtained. This study is in concordance with the Helsinki declaration.

Pediatric Health Information System Database

Data for this study were obtained from the Pediatric Health Information System (PHIS) database. PHIS is an administrative and billing database that contains inpatient, emergency department, ambulatory surgery, and observation data from not-for-profit, tertiary care pediatric hospitals in the United States. The 53 hospitals that contribute data to PHIS are affiliated with the Children's Hospital Association (Lenexa, KS), a business alliance of children's hospitals. Data quality and reliability are assured through a joint effort between the Children's Hospital Association and participating hospitals. For the purposes of external benchmarking, participating hospitals provide discharge/encounter data including demographics, diagnoses, procedures, and charges. Data are de-identified at the time of data submission, and data are subjected to a number of reliability and validity checks before being included in the database.

Admission Identification

Pediatric Health Information System database data from 2004 to 2015 were utilized for this study.

Firstly, admissions with cardiac diagnoses were identified. Online Resource 1 outlines the cardiac diagnoses which ultimately were eligible for consideration. Of these admissions, those with cardiac surgery were identified. Of these, admissions with chylothorax were then identified. Thus, the inclusion criteria for admissions for this study were (a) pediatric admissions under 18 years of age; (b) a cardiac diagnosis; (c) cardiac surgery; (d) chylothorax. Any admissions not meeting these criteria were excluded. From this point forward, the word "admission" will be used to refer to admissions meeting these inclusion criteria unless otherwise specified.

The admissions were then separated into two groups: (a) those that did not require surgical intervention for chylothorax; (b) those that did require surgical intervention for chylothorax. Surgical intervention was defined as either pleurodesis or thoracic duct ligation. The term "surgical intervention" will be used throughout the manuscript and will refer to either pleurodesis or thoracic duct ligation for chylothorax.

Chylothorax Interventions of Interest

The following medical therapies were considered as medical interventions for chylothorax: hydrocortisone, prednisone, dexamethasone, methylprednisolone, furosemide, acetazolamide, chlorothiazide, bumetanide, spironolactone, octreotide, propranolol, ibuprofen, ketorolac, diet of medium-chain triglycerides, and parenteral nutrition.

Admission Characteristics

Several data points were captured for each of the included admissions. Age of admission, gender, and year of admission were captured for all admissions. Length of stay, billed charges, and inpatient mortality were also recorded for all admissions. Any use of "mortality" from here on after will refer to inpatient mortality during the admission of interest.

The specific congenital heart malformations were captured using the ICD-9 codes outlined in Online Resource 1. The specific cardiac surgeries during the admissions were also captured using the ICD-9 codes outlined in Online Resource 1.

The presence or absence of the following comorbidities was recorded as well: heart failure, tachyarrhythmia, bradyarrhythmia, acute kidney injury, pulmonary hypertension, hypothyroidism, and the presence of syndromes.

Statistical Analyses

Continuous variables were described as median and range, while categorical variables were described as absolute frequency and percentage. Analyses of continuous variables across groups were conducted using a Mann–Whitney-*U* test, while analyses of categorical variables were conducted using a Fisher's exact test.

Characteristics between admissions that did and did not require surgical intervention for chylothorax were compared initially with univariate analyses.

Next, regression analyses were conducted to determine the impact of the various medical and surgical chylothorax interventions on intensive care unit length of stay, hospital length of stay, billed charges, and inpatient mortality. Additionally, the impact of various medical interventions on need for surgical intervention was also assessed. Logistic regressions were utilized for surgical intervention for chylothorax and inpatient mortality. Linear regressions were utilized for lengths of stay and billed charges. The dependent variable was one of the aforementioned outcomes while the independent variables included congenital cardiac malformations, the comorbidities previously mentioned, and the various medical and surgical interventions for chylothorax previously defined as being of interest. Center was included in all the regression analyses to account for any confounding that could occur due to variability in practice at different centers.

All statistical analyses were conducted using SPSS, Version 23.0. A p value of less than 0.05 was considered statistically significant. Any use of the word "significant" throughout this manuscript implies statistical significance unless otherwise specified.

Results

Univariate Comparison of Admissions With and Without Surgical Intervention for Chylothorax

A total of 3,503 patients were included in the final analyses. Of these, 236 (6.7%) required surgical intervention. Gender and age did not differ between the two groups. With respect to cardiac diagnoses, frequency of surgical intervention was only statistically different in those with d-transposition in which setting the odds ratio of surgical intervention was 1.7 (95% confidence interval 1.2–2.5). With respect to cardiac surgeries, frequency for surgical intervention for chylothorax was only statistically different in association with the following cardiac surgeries: mitral valvuloplasty without replacement (odds ratio 1.9, 95% confidence interval 1.1–3.5) and arterial switch (odds ratio 2.0, 95% confidence interval 1.4–3.0) (Table 1).

With respect to comorbidities, acute kidney injury (odds ratio 2.1, 95% confidence interval 1.5–2.9) and the need for dialysis (odds ratio 2.1, 95% confidence interval 1.2–3.5) were both associated with increased odds of surgical intervention. Cardiac arrest (odds ratio 1.7, 95% confidence interval 1.1–2.6) and extracorporeal membrane oxygenation (odds ratio 1.5, 95% confidence interval 1.1–2.2) were also associated with increased odds of surgical intervention (Table 1).

Intensive care unit length of stay, total hospital length of stay, billed charges, and mortality were also all greater in those with chylothorax requiring surgical intervention than those who did not require surgical intervention (Table 1). The frequency of various medical interventions for chylothorax by year is presented in Table 2.

Regression Analyses for Hydrocortisone

Regression analyses demonstrated the following regarding hydrocortisone in pediatric cardiac surgery admissions with chylothorax. Hydrocortisone was associated with a significant decrease in intensive care unit length of stay by 8.5 days ($p<0.01$) and significant decrease in billed charges by $193,872 ($p<0.01$). There was no significant association between hydrocortisone and total length of stay, need for surgical intervention, or mortality (Table 3).

Regression Analyses for Prednisone

Regression analyses demonstrated the following regarding prednisone in pediatric cardiac surgery admissions with chylothorax. Prednisone had no significant association with intensive care unit length of stay, total length of stay, billed charges, need for surgical intervention, or mortality (Table 3).

Regression Analyses for Dexamethasone

Regression analyses demonstrated the following regarding dexamethasone in pediatric cardiac surgery admissions with chylothorax. Dexamethasone was associated with a significant decrease in intensive care unit length of stay by 7.8 days ($p<0.01$), a significant decrease in total length of stay by 14.9 days ($p<0.01$), a significant decrease in billed charges by $197,416 ($p<0.01$), a significant decrease in need for surgical intervention (odds ratio 0.3, 95% confidence interval 0.1–0.8), and a significant decrease in mortality (odds ratio 0.2, 95% confidence interval 0.1–0.7) (Table 3).

Regression Analyses for Methylprednisolone

Regression analyses demonstrated the following regarding methylprednisolone in pediatric cardiac surgery admissions with chylothorax. Methylprednisolone was associated with a significant decrease in intensive care unit length of stay by 13.0 days ($p<0.01$), a significant decrease total length of stay by 22.2 days ($p<0.01$), a significant decrease in billed charges by $300,479 ($p<0.01$), a significant decrease in need for surgical intervention (odds ratio 0.2, 95% confidence interval 0.1–0.4), and a significant decrease in mortality (odds ratio 0.3, 95% confidence interval 0.1–0.7) (Table 3).

Regression Analyses for Furosemide

Regression analyses demonstrated the following regarding furosemide in pediatric cardiac surgery admissions with chylothorax. Furosemide was associated with a significant decrease in intensive care unit length of stay by 11.6 days ($p<0.01$), a significant decrease in total length of stay by 21.5 days, a significant decrease in billed charges by $307,963 ($p<0.01$), and a significant decrease in need for surgical intervention (odds ratio 0.1, 95% confidence interval 0.1–0.2). Furosemide had no significant association with mortality (Table 3).

Table 1 Univariate comparison of admissions with and without surgical intervention for chylothorax

	No chylothorax surgical intervention (*n* = 3267)	Chylothorax surgical intervention (*n* = 236)	Odds ratio (95% confidence interval)	*p* value
Gender (male)	1,924 (58.9)	134 (56.8)		0.78
Age (years)	0 (0–17)	0 (0–17)		0.79
Cardiac lesion				
Primum atrial septal defect	43 (1.3)	0 (0.0)	–	0.07
Secundum atrial septal defect	1,612 (49.3)	105 (44.5)	0.82 (0.63–1.07)	0.15
Ventricular septal defect	930 (28.5)	67 (28.4)	0.99 (0.74–1.33)	0.98
Double outlet right ventricle	412 (12.6)	23 (9.7)	0.74 (0.48–1.16)	0.19
Tetralogy of fallot	407 (12.5)	24 (10.2)	0.79 (0.51–1.22)	0.30
Pulmonary atresia	191 (5.8)	16 (6.8)	1.17 (0.69–1.98)	0.55
Atrioventricular septal defect	564 (17.3)	35 (14.8)	0.83 (0.57–1.20)	0.33
Transposition	344 (10.5)	41 (17.4)	1.78 (1.25–2.54)	< 0.01
Congenitally corrected transposition	60 (1.8)	4 (1.7)	0.92 (0.33–2.55)	0.87
Common arterial trunk	64 (2.0)	5 (2.1)	1.08 (0.43–2.71)	0.86
Ebstein anomaly	64 (2.0)	2 (0.8)	0.42 (0.10–1.75)	0.22
Hypoplastic left heart syndrome	858 (26.3)	72 (30.5)	1.23 (0.92–1.64)	0.15
Functionally univentricular heart other than HLHS	290 (8.9)	21 (8.9)	1.00 (0.63–1.59)	0.99
Coarctation of the aorta	406 (12.4)	29 (12.3)	0.98 (0.66–1.47)	0.95
Interrupted aortic arch	73 (2.2)	8 (3.4)	1.53 (0.73–3.22)	0.25
Partial anomalous pulmonary venous connection	63 (1.9)	2 (0.8)	0.43 (0.10–1.78)	0.23
Total anomalous pulmonary venous connection	207 (6.3)	16 (6.8)	1.07 (0.63–1.82)	0.78
Systemic venous anomaly	212 (6.5)	12 (5.1)	0.77 (0.42–1.40)	0.39
Congenital tricuspid stenosis	219 (6.7)	19 (8.1)	1.21 (0.74–1.98)	0.42
Congenital mitral stenosis	78 (2.4)	4 (1.7)	0.70 (0.25–1.94)	0.49
Congenital pulmonary stenosis	194 (5.9)	13 (5.5)	0.92 (0.51–1.64)	0.78
Congenital aortic stenosis	80 (2.4)	6 (2.5)	1.03 (0.44–2.40)	0.92
Congenital subaortic stenosis	59 (1.8)	1 (0.4)	0.23 (0.03–1.67)	0.11
Congenital pulmonary artery anomaly	274 (8.4)	19 (8.1)	0.95 (0.58–1.55)	0.85
Congenital coronary anomaly	156 (4.8)	7 (3.0)	0.61 (0.28–1.31)	0.20
Cardiac surgery				
Valvuloplasty without replacement, unspecified valve	7 (0.2)	0 (0.0)	–	0.47
Valvuloplasty without replacement, aortic valve	52 (1.6)	5 (2.1)	1.33 (0.52–3.38)	0.53
Valvuloplasty without replacement, mitral valve	95 (2.9)	13 (5.5)	1.94 (1.07–3.53)	0.02
Valvuloplasty without replacement, pulmonary valve	121 (3.7)	7 (3.0)	0.79 (0.36–1.72)	0.56
Valvuloplasty without replacement, tricuspid valve	206 (6.3)	13 (5.5)	0.86 (0.48–1.54)	0.62
Replacement, unspecified valve	0 (0.0)	0 (0.0)	–	–
Tissue replacement, aortic valve	26 (0.8)	3 (1.3)	1.60 (0.47–5.34)	0.43
Mechanical replacement, aortic valve	4 (0.1)	0 (0.0)	–	0.59
Tissue replacement, mitral valve	27 (0.8)	0 (0.0)	–	0.16
Mechanical replacement, mitral valve	7 (0.2)	0 (0.0)	–	0.47
Tissue replacement, pulmonary valve	34 (1.0)	4 (1.7)	1.63 (0.57–4.66)	0.34
Mechanical replacement, pulmonary valve	27 (0.8)	2 (0.8)	1.02 (0.24–4.33)	0.97
Tissue replacement, tricuspid valve	5 (0.2)	0 (0.0)	–	0.54
Mechanical replacement, tricuspid valve	6 (0.2)	2 (0.8)	4.64 (0.9–23.1)	0.06
Operation on papillary muscle	12 (0.4)	0 (0.0)	–	0.35
Operation on chordae tendineae	9 (0.3)	0 (0.0)	–	0.41
Annuloplasty	55 (1.7)	1 (0.4)	0.24 (0.03–1.80)	0.13
Infundibulectomy	61 (1.9)	5 (2.1)	1.13 (0.45–2.85)	0.78
Enlargement of existing atrial septal defect	341 (10.4)	35 (14.8)	1.49 (1.02–2.17)	0.03
Creation of septal defect	312 (9.6)	20 (8.5)	0.87 (0.54–1.40)	0.58

Table 1 (continued)

	No chylothorax surgical intervention ($n=3267$)	Chylothorax surgical intervention ($n=236$)	Odds ratio (95% confidence interval)	*p* value
Repair of atrial septal defect	35 (1.1)	5 (2.1)	1.99 (0.77–5.15)	0.14
Repair of ventricular septal defect with prosthesis	208 (6.4)	10 (4.2)	0.65 (0.34–1.24)	0.19
Repair of ventricular septal defect with tissue	269 (8.2)	11 (4.7)	0.54 (0.29–1.01)	0.05
Repair of atrioventricular septal defect with prosthesis	113 (3.5)	6 (2.5)	0.72 (0.31–1.67)	0.45
Repair of atrioventricular septal defect with tissue	231 (7.1)	11 (4.7)	0.64 (0.34–1.19)	0.15
Total repair of tetralogy of Fallot	323 (9.9)	15 (6.4)	0.61 (0.36–1.05)	0.07
Total repair of anomalous pulmonary venous connection	174 (5.3)	13 (5.5)	1.03 (0.58–1.85)	0.90
Total repair of common arterial trunk	59 (1.8)	3 (1.3)	0.70 (0.21–2.25)	0.54
Arterial switch	238 (7.3)	33 (14.0)	2.06 (1.49–3.05)	< 0.01
Atrial switch	58 (1.8)	3 (1.3)	0.71 (0.22–2.29)	0.56
Right ventricle–pulmonary artery conduit	350 (10.7)	19 (8.1)	0.73 (0.45–1.18)	0.19
Heart transplant	116 (3.6)	13 (5.5)	1.58 (0.87–2.85)	0.12
Systemic to pulmonary artery shunt	600 (18.4)	43 (18.2)	0.99 (0.70–1.39)	0.95
Glenn	638 (19.5)	39 (16.5)	0.81 (0.57–1.16)	0.25
Fontan	453 (13.9)	41 (17.4)	1.30 (0.91–1.85)	0.13
Syndrome	662 (20.3)	40 (16.9)	0.80 (0.56–1.14)	0.21
Heart failure	237 (7.3)	18 (7.6)	1.05 (0.64–1.73)	0.83
Tachyarrhythmia	498 (15.2)	40 (16.9)	1.13 (0.79–1.61)	0.48
Bradyarrhythmia	426 (13.0)	23 (9.7)	0.72 (0.46–1.12)	0.14
Acute kidney injury	462 (14.1)	62 (26.3)	2.16 (1.59–2.93)	< 0.01
Need for dialysis	129 (3.9)	19 (8.1)	2.13 (1.29–3.51)	< 0.01
Pulmonary hypertension	450 (13.8)	35 (14.8)	1.09 (0.75–1.58)	0.65
Cardiac arrest	194 (5.9)	23 (9.7)	1.71 (1.08–2.69)	0.01
Extracorporeal membrane oxygenation	338 (10.3)	36 (15.3)	1.56 (1.07–2.26)	0.01
ICU length of stay	13 (0–470)	38 (0–359)	–	< 0.01
Total length of stay	31 (1–568)	70 (14–482)	–	< 0.01
Billed charges	441,954	1,031,709	–	< 0.01
Inpatient mortality	254 (7.8)	56 (23.7)	3.69 (2.66–5.11)	< 0.01

HLHS Hypoplastic left heart syndrome, *ICU* intensive care unit

Table 2 Frequency of medical interventions by year

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total	*p* value
Hydrocortisone	3.9%	3.6%	5.5%	6.2%	4.9%	2.5%	4.3%	5.3%	4.5%	6.0%	4.6%	6.0%	4.9%	0.67
Prednisone	0.8%	0.0%	0.0%	0.4%	0.3%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.38
Dexamethasone	12.4%	10.2%	15.7%	15.1%	12.9%	13.1%	10.8%	8.5%	11.9%	15.1%	13.0%	11.4%	12.4%	0.24
Methylprednisolone	14.0%	19.8%	22.1%	22.0%	19.4%	19.7%	24.4%	23.0%	23.1%	16.2%	15.1%	13.9%	19.4%	< 0.01
Furosemide	79.1%	80.2%	80.6%	80.7%	81.6%	85.6%	85.2%	80.7%	78.5%	81.9%	84.9%	90.4%	82.9%	< 0.01
Acetazolamide	1.0%	0.0%	1.4%	1.2%	0.0%	1.3%	0.9%	0.8%	1.3%	1.4%	0.5%	0.3%	0.8%	0.57
Chlorothiazide	4.7%	10.8%	7.8%	10.8%	10.0%	7.2%	8.3%	11.6%	11.2%	11.5%	9.0%	7.8%	9.5%	0.25
Propranolol	8.5%	5.4%	3.7%	6.6%	11.3%	6.3%	13.0%	8.2%	12.5%	11.0%	9.0%	11.1%	9.2%	< 0.01
Ibuprofen	29.5%	37.1%	39.2%	34.0%	27.5%	33.4%	36.7%	33.3%	29.2%	28.2%	26.6%	24.4%	31.1%	< 0.01
Ketorolac	18.6%	24.0%	30.0%	17.0%	24.3%	20.3%	21.6%	25.9%	24.4%	29.3%	27.9%	21.4%	24.1%	< 0.01

Regression Analyses for Acetazolamide

Acetazolamide had no significant association with any of the endpoints of interest.

Table 3 Regression analysis of the impact of various medical and surgical interventions in intensive care unit and hospital length of stay, billed charges, surgical interventions for chylothorax, and mortality

ICU length of stay (BC, *p* value)	Total length of stay (BC, *p* value)	Billed charges (BC, *p* value)	Surgical intervention for chylothorax (OR, 95% CI)	Mortality (OR, 95% CI)
Hydrocortisone (− 8.5, $p<0.01$)	Hydrocortisone (− 6.9, $p=0.06$)	Hydrocortisone (− 193,872, $p<0.01$)	Hydrocortisone (0.8, 0.3–2.1)	Hydrocortisone (1.9, 0.8–4.4)
Prednisone (0.9, $p=0.96$)	Prednisone (0.4, $p=0.94$)	Prednisone (− 6,453, $p=0.98$)	Prednisone (0.4, 0.1–1.4)	Prednisone (1.4, 0.4–1.9)
Dexamethasone (− 7.8, $p<0.01$)	Dexamethasone (− 14.9, $p<0.01$)	Dexamethasone (− 197,416, $p<0.01$)	Dexamethasone (0.3, 0.1–0.8)	Dexamethasone (0.2, 0.1–0.7)
Methylprednisolone (− 13.0, $p<0.01$)	Methylprednisolone (− 22.2, $p<0.01$)	Methylprednisolone (− 300,479, $p<0.01$)	Methylprednisolone (0.2, 0.1–0.4)	Methylprednisolone (0.3, 0.1–0.7)
Furosemide (− 11.6, $p<0.01$)	Furosemide (− 21.5, $p<0.01$)	Furosemide (− 307,963, $p<0.01$)	Furosemide (0.1, 0.1–0.2)	Furosemide (0.5, 0.1–1.5)
Acetazolamide (2.0, $p=0.77$)	Acetazolamide (4.0, $p=0.64$)	Acetazolamide (38,606, $p=0.82$)	Acetazolamide (0.7, 0.4–2.5)	Acetazolamide (0.8, 0.6–3.2)
Chlorothiazide (− 3.4, $p=0.19$)	Chlorothiazide (− 3.9, $p=0.23$)	Chlorothiazide (− 84,545, $p=0.18$)	Chlorothiazide (0.6, 0.1–2.2)	Chlorothiazide (0.2, 0.1–1.6)
Bumetanide (− 0.3, $p=0.97$)	Bumetanide (− 2.9, $p=0.79$)	Bumetanide (− 3,225, $p=0.98$)	Bumetanide (0.8, 0.3–1.9)	Bumetanide (0.9, 0.4–1.3)
Spironolactone (0.1, $p=0.95$)	Spironolactone (2.6, $p=0.52$)	Spironolactone (46,378, $p=0.55$)	Spironolactone (13.6, 0.6–282.4)	Spironolactone (0.7, 0.3–1.5)
Octreotide (− 8.1, $p=0.09$)	Octreotide (− 6.1, $p=0.31$)	Octreotide (− 163,315, $p=0.16$)	Octreotide (7.0, 3.1–15.9)	Octreotide (1.9, 0.5–6.3)
Propranolol (− 5.9, $p<0.01$)	Propranolol (− 2.4, $p=0.37$)	Propranolol (− 167,127, $p<0.01$)	Propranolol (0.6, 0.3–1.1)	Propranolol (0.7, 0.4–1.1)
Ibuprofen (7.8, <0.01)	Ibuprofen (12.4 ($p<0.01$)	Ibuprofen (261,747, $p<0.01$)	Ibuprofen (1.0, 0.7–1.5)	Ibuprofen (0.9, 0.6–1.2)
Ketorolac (− 5.6, $p<0.01$)	Ketorolac (− 12.9, $p<0.01$)	Ketorolac (− 267,086, $p<0.01$)	Ketorolac (1.0, 0.7–1.4)	Ketorolac (0.5, 0.3–0.7)
MCT (− 7.3, $p=0.19$)	MCT (− 10.8, $p=0.10$)	MCT (− 190,068, $p=0.13$)	MCT (0.5 0.1–1.8)	MCT (0.3, 0.1–2.4)
Parenteral nutrition (1.4, $p=0.30$)	Parenteral nutrition (8.8. $p<0.01$)	Parenteral nutrition (295,224, $p<0.01$)	Parenteral nutrition (1.3, 0.9–1.7)	Parenteral nutrition (1.2, 0.8–1.6)
Pleurodesis (14.2, $p<0.01$)	Pleurodesis (20.4, $p<0.01$)	Pleurodesis (289,979, $p<0.01$)		Pleurodesis (1.8, 0.8–3.8)
Thoracic duct ligation (23.7, $p<0.01$)	Thoracic duct ligation (29.3, $p<0.01$)	Thoracic duct ligation (423,774, $p<0.01$)		Thoracic duct ligation (2.9, 1.9–4.4)

ICU Intensive care unit, *BC* beta coefficient, *OR* odds ratio, *CI* confidence interval, *MCT* medium-chain triglycerides

Regression Analyses for Chlorothiazide

Chlorothiazide had no significant association with any of the endpoints of interest.

Regression Analyses for Bumetanide

Bumetanide had no significant association with any of the endpoints of interest.

Regression Analyses for Spironolactone

Spironolactone had no significant association with any of the endpoints of interest.

Regression Analyses for Octreotide

Octreotide had no significant association with any of the endpoints of the interest.

Regression Analyses for Propranolol

Regression analyses demonstrated the following regarding propranolol in pediatric cardiac surgery admissions with chylothorax. Propranolol was associated with a significant decrease in intensive care unit length of stay by 5.9 days ($p<0.01$) and a decrease in billed charges by \$167,127 ($p<0.01$). Propranolol had no significant association with total length of stay, need for surgical intervention, or mortality.

Regression Analyses for Ibuprofen

Regression analyses demonstrated the following regarding ibuprofen in pediatric cardiac surgery admissions with chylothorax. Ibuprofen was associated with a significant increase in intensive care unit length of stay by 7.8 days ($p < 0.01$), an increase in total length of stay by 12.4 days ($p < 0.01$), an increase in billed charges by $261,747 ($p < 0.01$). Ibuprofen had no significant association with need for surgical intervention or mortality.

Regression Analyses for Ketorolac

Regression analyses demonstrated the following regarding ketorolac in pediatric cardiac surgery admissions with chylothorax. Ketorolac was associated with significant decrease in intensive care unit length of stay by 5.6 days ($p < 0.01$), a decrease in total length of stay by 12.9 days ($p < 0.01$), a decrease in billed charges by $267,086 ($p < 0.01$). Ketorolac had no significant association with need for surgical intervention or mortality.

Regression Analyses for Medium-Chain Triglycerides

Medium-chain triglycerides had no significant association with any of the endpoints of interest.

Regression Analyses for Parenteral Nutrition

Regression analyses demonstrated the following regarding parenteral nutrition in pediatric cardiac surgery admissions with chylothorax. Parenteral nutrition was associated with a significant increase in total length of stay by 8.8 days ($p < 0.01$) and a significant increase in billed charges by $292,224 ($p < 0.01$). Parenteral nutrition had no significant association with intensive care unit length of stay, need for surgical intervention, or mortality.

Regression Analyses for Pleurodesis

Regression analyses demonstrated the following regarding pleurodesis in pediatric cardiac surgery admissions with chylothorax. Pleurodesis was associated with a significant increase in intensive care unit length of stay by 14.2 days ($p < 0.01$), a significant increase in total length of stay by 20.4 days ($p < 0.01$), and a significant increase in billed charges by $289,979 ($p < 0.01$). Pleurodesis had no significant association with mortality (Table 3).

Regression Analyses for Thoracic Duct Ligation

Regression analyses demonstrated the following regarding thoracic duct ligation in pediatric cardiac surgery admissions with chylothorax. Thoracic duct ligation was significantly associated with an increase in intensive care unit length of stay by 23.7 days ($p < 0.01$), a significant increase in total length of stay by 29.3 days ($p < 0.01$), a significant increase in billed charges by $423,774 ($p < 0.01$), and a significant increase in mortality (odds ratio 2.9, 95% confidence interval 1.9–4.4).

Discussion

Frequency of chylothorax after pediatric cardiac surgery has been found to be anywhere from 1 to 9%, with several studies reporting a frequency in the middle of this range [1–3]. While this frequency is low, the presence of chylothorax in pediatric cardiac surgery admissions greatly increases resource utilization [6–9].

Previous studies have demonstrated that chylothorax in pediatric admissions after cardiac surgery is more frequent in admissions with aortic surgery and functionally univentricular surgery [10]. Additionally, those with higher central venous pressures, venous thrombosis, and syndromes are also more likely to have chylothorax [5, 11–15]. Trauma to the lymphatic vessels may also lead to chylothorax [16]. Chylothorax may either be the result of increased lymphatic fluid production, decreased lymphatic transport, or both [17].

This set of analyses using data from the Pediatric Health Information System database set forth to characterize the population of pediatric cardiac surgery patients with chylothorax who eventually require pleurodesis and/or thoracic duct ligation and to try to establish some objective data on the impact of various medical interventions on admission characteristics.

A total of 3503 pediatric admissions with cardiac surgery and subsequent chylothorax were included. Of these, 236 (6.7%) required surgical intervention for the chylothorax. The following cardiac diagnoses, cardiac surgeries, and comorbidities were associated with increased odds of surgical intervention: d-transposition, arterial switch, mitral valvuloplasty, acute kidney injury, need for dialysis, cardiac arrest, and extracorporeal membrane oxygenation.

Interestingly, mitral valve replacement, tissue or mechanical, was not associated with chylothorax despite mitral valvuloplasty having a positive association. One explanation is that mitral valvuloplasty is preferred to valve replacement in a very young patient due to the need for future upsizing of the valve (illustrated by the higher number of mitral valvuloplasties compared to replacements). D-transposition and arterial switch operations, both associated with the neonatal period, are also significantly associated with chylothorax. Both mitral valve lesions and d-transposition are associated with younger age and are at risk for elevated pulmonary artery pressures in the post-operative period.

More importantly, these analyses also demonstrated the impact of interventions for chylothorax on admission characteristics. Specific steroids (hydrocortisone, dexamethasone, methylprednisolone) and specific diuretics (furosemide) were significantly associated with decreased intensive care unit and hospital lengths of stay and billed charges. Dexamethasone, methylprednisolone, and furosemide were associated with decreased odds for surgical intervention. Dexamethasone and methylprednisolone were also associated with decreased odds for mortality in those with chylothorax. Nutritional interventions such as high medium chain/long chain triglyceride restricted diet and parenteral nutrition were not significantly associated with improvements in admission characteristics and did not decrease the odds for surgical intervention or mortality. Parenteral nutrition was associated with increased total length of stay and increased billed charges. Octreotide was found to have no significant impact.

These are the first analyses we can identify that try to identify specific diagnoses, surgeries, and comorbidities associated with increased need for surgical intervention for chylothorax. Additionally, this is the largest set of analyses that attempts to delineate the utility of specific medical interventions in those with chylothorax. Previous reports are mostly case reports or descriptive cohort studies [18].

Institutions have developed clinical protocols for the management of chylothorax. These protocols are based on case reports, descriptive cohort studies, or anecdotal evidence and, thus, practice patterns vastly differ by provider or institution [4, 5].

Many centers begin by diet modification when a chylothorax is noted. Many centers will transition to medium chain triglyceride-based formulas or long chain triglyceride restriction [16]. Overall, this is a rather benign intervention. While other case series have reported success with these interventions, the current analyses demonstrate that this intervention is not significantly associated with any change in need for surgical intervention, mortality, or any other of the admission characteristics. The association, although insignificant, is in a helpful direction with positive reductions in lengths of stay, billed charges, need for surgical intervention, and mortality. Thus, medium chain triglyceride-based diet with long chain triglyceride restrictions still seems like a reasonable early intervention, although it likely serves a greater nutritional purpose, particularly in those who are on low-fat diets.

Another diet modification some will utilize is allowing no oral intake and switching to parenteral nutrition. Several institutions still utilize parenteral nutrition in conjunction with nothing by mouth in pediatric admissions with chylothorax after cardiac surgery [2, 19, 20]. Parenteral nutrition does not ameliorate hunger and is expensive. These analyses demonstrate that parenteral nutrition does not positively impact admission characteristics. In fact, parenteral nutrition was found to be associated with a significant increase in total length of stay and billed charges. It seems that switching to parenteral nutrition is unlikely to be beneficial in children with chylothorax after cardiac surgery. This study's findings are in agreement with results reported by Church and colleagues that no oral intake with only parenteral nutrition in a study of 178 neonates with chylothorax does not positively effect chylothorax outcomes [20].

Dietary modifications are believed to be helpful in the presence of chylothorax as minimizing long chain triglycerides is believed to reduce the amount of flow and distension to an injured lymphatic vessel. Previous studies have demonstrated that chylous drainage is mostly long chain fats. Thus, it was anecdotally believed that minimizing long chain fats and supplementing medium chain triglycerides would be helpful in decreasing chylous draining. Some have reported as such [18, 21]. This has not necessarily been shown to be the case, and Jensen and colleagues have demonstrated in patients with predominantly medium chain triglyceride intake that chylous drainage may not decrease but rather the composition simply may change. Thus, the findings of these analyses that medium chain triglyceride-based diet does not significantly change the need for surgical intervention or mortality are not entirely surprising. Due to the relative ease of instituting a low-fat diet and medium chain triglyceride supplementation, it may be reasonable to still attempt this, understanding that the results of these analyses demonstrate an insignificant association towards improvement in the admission characteristics of interest.

However, it is worth noting that the institution of a fat restricted diet is not a completely benign therapy. The nutrient losses associated with chylothorax as well as a diet restricted in vital nutrients further increases the risk of poor growth and poor wound healing in already at-risk population. While children older than 1 year of age who eat by mouth may be able to sufficiently nourish themselves with their oral diet, children who do not eat by mouth require the use of medically modified formulas. Similarly, infants also require supplementation, if not sole nutrition, from medically modified formulas restricted in long chain triglycerides. While skimming or defatting human milk in the presence of chylothorax has shown to be a successful dietary modification, it is associated with decreased growth and still requires the use of medium chain triglyceride-based formulas for supplementation. Furthermore, defatting or skimming human milk may not always be an option for an infant with chylothorax, necessitating a medium chain triglyceride-based formula as their sole nutrition source. These formulas are expensive, not as readily available as other standard formulas and/or breastmilk, are associated with poor growth and feeding intolerance, and are deficient in necessary nutrients for growth and development. Additionally, there is plenty of anecdotal information based on caregiver and clinician experience with these formulas indicating decreased oral intake and increased irritability and feeding intolerance. While dietary modification for the treatment of chylothorax has made great strides, it is still associated with poor feeding tolerance and poor growth [21].

Diuresis is utilized a great deal in the cardiac intensive care unit. The current analyses looked at various diuretics to determine if any had a positive impact on admission characteristics. Furosemide positively impacted admission characteristics, being associated with decreases in lengths of stay, billed charges, need for surgical intervention, and mortality. None of the other diuretics had a significant association with admission characteristics.

The utility of diuretics becomes evident as diuretics will decrease the overall fluid that needs to be drained through the lymphatic system. Also, as a function of decreased circulating volume, diuretics also decrease the central venous pressure to help maintain a pressure gradient between the lymphatic circulation and systemic venous circulation so as to not impair drainage of the lymphatic circulation into the systemic venous circulation. Furosemide is usually the first line diuretic used prior to adding second line agents such as chlorothiazide. This study suggests that furosemide alone is already a very effective diuretic, and the addition of additional diuretics is of little benefit in decreasing circulating volume and improving chylothorax outcomes.

Next, the current set of analyses modeled the association of various steroids on admission characteristics. Of the steroids that were analyzed, hydrocortisone, dexamethasone, and methylprednisolone were associated with significant reductions in lengths of stay and billed charges. Only dexamethasone and methylprednisolone were associated with significant decrease in need for surgical intervention and mortality as well. Thus, it appears that steroids do have a role in management of pediatric admissions with chylothorax after cardiac surgery.

The role of steroids in improving chylothorax outcomes is less clear. Post-operative inflammation may irritate the lymphatic system leading to increased leak out of the lymphatic circulation. Goldstein et al. found increased pro-inflammatory cytokine levels such as TNF-α in post-operative Fontan pleural drainage that rises over time suggesting the possibility of ongoing, localized inflammation. Thus, steroids may blunt some of this inflammatory response and the subsequent lymphatic leak.

Octreotide was found to not have any significant association with any of the admission characteristics. Of note, however, similar to medium-chain triglyceride diet with long-chain triglyceride restriction, the direction of association for octreotide with the admission characteristics of interest were favorable, although statistically insignificant. Small studies have reported benefit of octreotide in the past, although some of this was anecdotally based from case reviews rather than statistical analyses [2, 18, 22, 23]. The aforementioned study by Church et al. also demonstrated no benefit in the use of octreotide [20].

When all medical interventions are reviewed for significant positive impact on chylothorax, the following hierarchy seems to emerge with the first being the most beneficial: methylprednisolone, dexamethasone, furosemide, hydrocortisone, ketorolac, and then propranolol. The rationale behind this ranking is as follows: (a) only dexamethasone and methylprednisolone had a significant beneficial association with all five admission characteristics so they immediately were slotted in the first and second slots; (b) methylprednisolone had the most absolute impact by comparison of beta-coefficients resulting from the regression analyses, and thus was ranked higher than dexamethasone; (c) furosemide and hydrocortisone both had a significant beneficial association with the same four of five admission characteristics and then were ranked by comparing the absolute effect based on beta-coefficients resulting from the regression analyses; (d) ketorolac had a significant beneficial association with three of five admission characteristics; (e) propranolol had significant beneficial association with two of five admission characteristics.

It seems reasonable from these data to initiate treatment of post-operative chylothorax with diuresis with furosemide. As other diuretics did not demonstrate significant associations with any of the admission characteristics, maximizing furosemide dose prior to adding a second agent may be prudent. Next, it seems reasonable to begin a treatment course of methylprednisolone or dexamethasone, according to provider preference such as treating concomitant airway inflammation, once a chylothorax is diagnosed. Low-fat diets could not be directly analyzed in this study and switching to a low-fat diet may also be done. Medium-chain triglyceride diets with long-chain triglyceride restrictions and octreotide do not seem to be of help. Parenteral nutrition appears to offer no particular benefit in the management of chylothorax. For refractory chylothorax, surgical intervention may be necessary.

Results from this study seem to indicate that most post-operative chylothoraxes should improve with furosemide, a low-fat diet, and steroids. Interestingly, a study by Jensen and colleagues demonstrated that those who did respond to initial intervention with diet changes tended to be those with already decreasing chylous draining, leading the authors to believe that resolution was spontaneous and time dependent anyway [24]. Nonetheless, the current analyses have shown benefit to steroids and diuretic in pediatric cardiac surgery admissions with chylothorax.

These analyses offer one of the largest collections of objective data regarding the effects of interventions for chylothorax in pediatric cardiac surgery admissions. The large number of patients allows for reasonable statistical power as well. In light of the current paucity of evidence, these data should be helpful in guiding clinical management. Nonetheless, these analyses are not without limitations. Firstly, this a retrospective study and thus only association and not causation can be analyzed. Causality is not being implied by any of the aforementioned statistical analyses. The duration, dose, and timing of interventions cannot be ascertained. These may be valuable variables and can impact the associations of interventions with the admission characteristics. Additionally, administrative databases are prone to errors in data collection secondary to improper coding and under coding. Also, severity of illness can be difficult to assess from an administrative database such as PHIS where laboratory or hemodynamic values are not captured. We have attempted to account for this by including multiple comorbidities such as heart failure, acute kidney injury, arrhythmias, and cardiac arrest to serve as a surrogate marker for severity of illness. Additionally, center was included as an independent variable in the regression analyses. Confounding by intention is also very likely present in these analyses. Overcoming this is difficult, statistically.

Future studies utilizing such a protocol and comparing them to other methods of chylothorax management can further help delineate the validity of this approach to management of chylothorax in pediatric cardiac surgery admissions based on the data from these analyses. Institutional protocols should also change with time to compare various medical interventions in a controlled fashion. Nonetheless, these current analyses provide pilot data to help hypothesis generation but are not definitive data due to the study design utilized which is prone to confounding by indication.

Conclusion

When various diuretics, steroids, dietary modifications, and octreotide are analyzed for effect on intensive care unit length of stay, total length of stay, billed charges, need for surgical intervention for chylothorax, and inpatient mortality, the following interventions are found to be associated with significant improvement in admission characteristics from greatest to least benefit: methylprednisolone, dexamethasone, hydrocortisone, and furosemide. Other diuretics, other steroids, parenteral nutrition, and medium-chain triglyceride diets with long-chain triglyceride restriction were not associated with significant improvement in any of the admission characteristics of interest.

Acknowledgments None.

Author Contributions RSL, SF, and JW contributed to the study conception and design. Material preparation, data collection, and analysis were performed by JSF, EGV, BH, and SK. The first draft of the manuscript was written by JW, MD, and RSL. SF commented on previous versions of the manuscript. All authors read and approved the final manuscript. Reviewing and editing was done by RSL and EGV.

Funding This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data Availability All data and materials, as well as software application, support our published claims and comply with field standards.

Compliance with Ethical Standards

Conflict of Interests The authors declare that they have no conflict of interest.

Human Rights The Study have been approved by the appropriate institutional ethics committee and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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