Prediction Model with External Validation for Early Detection of Postoperative Pediatric Chylothorax

Rohin Moza (rohin.moza@hsc.utah.edu)
University of Utah / Primary Children's Hospital
Melissa Winder NP
University of Utah / Primary Children's Hospital
Gregory T. Adamson
Stanford University / Lucile Packard Children's Hospital
Zhining Ou
University of Utah
Angela P. Presson
University of Utah
Senthuran Vijayarajah
University of Oklahoma Health Sciences Center
Stephanie A. Goldstein
University of Utah / Primary Children's Hospital
David K. Bailly
University of Utah / Primary Children's Hospital

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Abstract

Background: Earlier diagnosis of chylothorax following pediatric cardiac surgery is associated with decreased duration of chylothorax. Pleural fluid testing is used to diagnosis chylothorax which may delay detection in patients who are not enterally fed at time of chylothorax onset. Our aim was to develop and externally validate a prediction model to detect chylothorax earlier than pleural fluid testing in pediatric patients following cardiac surgery.

Methods: A Multivariable logistic regression model was developed to detect chylothorax using a step-wise approach. The model was developed using data from patients <18 years following cardiac surgery from Primary Children's Hospital, a tertiary-care academic center, between 2017 and 2020. External validation used a contemporary cohort (n=171) from Lucille Packard Children's Hospital.

Results: A total of 763 encounters (735 patients) were analyzed, of which 72 had chylothorax. The final variables selected were chest tube output (CTO) the day after sternal closure (dichotomized at 15.6 mL/kg/day, and as a continuous variable) and delayed sternal closure. The highest odds of chylothorax was associated with CTO on post sternal closure day 1 >15.6mL/kg/day (odds ratio 11.3, 95% CI 6,3, 21.3). The c-statistic for the internal and external validation datasets using the dichotomized CTO variable were 0.78 (95% CI:0.73, 0.82) and 0.84 (95% CI, 0.78, 0.9) and performance improved when using CTO as a continuous variable (OR 0.84, CI: 95% CI 0.80, 0.87)

Conclusions: Using the models described, chylothorax after pediatric cardiac surgery may be detected earlier and without reliance on enteral feeds.

Introduction

The complications associated with chylothorax following pediatric cardiac surgery include increased mortality, length of stay (LOS), cost, malnutrition, central line dependence, thrombosis, and infections.[1-12] These adverse associations are exacerbated by increased chylothorax duration.

Importantly, earlier diagnosis of chylothorax is associated with decreased duration of chylothorax, highlighting the benefit of early detection.[5] Furthermore, variation exists in reported median time from operating room to chylothorax diagnosis ranging between 4-9 days.[1, 3, 5, 11] Pleural fluid analysis for triglycerides and lymphocytes is currently the most widely accepted method for diagnosis of chylothorax. [13-18] However, the sensitivity of pleural fluid accuracy depends on production lymph which often requires enteral delivery of fat. Hence, early detection using pleural fluid testing is currently limited by timing of initiation of postoperative enteral feeds.

In this study, we aim to develop and externally validate a prediction model to detect chylothorax earlier than traditional pleural fluid testing.

Patients And Methods

Study design and participants

Patients < 18 years of age who underwent cardiac surgery at Primary Children's Hospital, a tertiary-care center in Salt Lake City, UT, between October 2017 and February 2020 were eligible. Patients were excluded from analysis if they received extracorporeal mechanical circulatory support or if they were diagnosed with chylothorax that resolved within one day of chest closure. Surgical encounters within 30 days of a previous chylothorax diagnosis were excluded as they may have still been receiving treatment for chylothorax previously associated with a surgery. The patient standard of care was not altered.

Our primary outcome was chylothorax, which was identified by pleural fluid triglycerides >110 mg/dL, pleural fluid lymphocytes >80%, and/or pleural fluid triglycerides > serum triglycerides.

The study was approved with a waiver of informed consent granted by the University of Utah Institutional Review Board and Primary Children's Hospital Private Board, and we adhered to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement. [19]

Variable definitions

The variables collected were defined as per the PC^4 data dictionary including a composite variable of genetic condition that included genetic syndromes, extracardiac anomalies and other unspecified conditions (https://pc4.arbormetrix.com/). Chest closure is defined by the day of primary or secondary delayed chest closure. Post-closure day (PCD) is defined by the number of days after chest closure, with day 0 being the date of chest closure. CTO is defined as the total volume of pleural fluid measured in mL/kg in 24 hours. Single or biventricular repair was classified independently by two authors, DB and MW, with a discussion to achieve consensus as needed.

Candidate predictors

We considered CTO volume on PCD 1 (06:00 the day after closure through 06:00 the following day) as a predictor, which was analyzed as a dichotomous, linear, and non-linear variable. Although CTO on PCD 0 would allow for earlier prediction, we excluded it due to potential confounders of fluid irrigation and bleeding which may be common on PCD 0.

The remainder of candidate predictors have been previously identified as risk factors for chylothorax which include age and weight at surgery, race, gender, presence of genetic condition, surgical STAT (Society of Thoracic Surgeons—European Association for Cardio-Thoracic Surgery) category,[20] single or biventricular repair with or without arch reconstruction, cardiopulmonary bypass (CPB) time in minutes, delayed sternal closure (DSC), and prior cardiothoracic surgery, [8, 12, 21-24]

Statistical analysis

We summarized demographics and clinical outcomes using median and interquartile range (IQR) for the continuous variables, and we reported counts and percentages for the categorical variables. We compared variables in those with and without chylothorax using nonparametric Wilcoxon rank sum tests for continuous variables, and chi-squared or Fisher's exact test for categorical variables.

Separate models were developed for each classification of CTO on PCD 1 (Model A = dichotomous, Model B = linear function, and Model C = non-linear function). Model D excluded all classifications of CTO on PCD 1. Chest tube output on PCD 1 was dichotomized at 15.6 mL/kg/day based on a threshold estimated from Youden's J statistic, which considers the specificity and sensitivity between the predicted and true chylothorax diagnosis to have equal importance.[25] Non-linear analysis of CTO on PCD 1 was modeled as a piecewise polynomial natural cubic spline function with 5 equally spaced knots. Variables associated with chylothorax ($p < 0.10$) were included in the multivariate model building with the exception of age which was excluded due to collinearity with weight. Model A retained CTO on PCD 1 as a dichotomized variable, DSC and CPB. Due to minimal improvement in data fit; Akaike Information Criteria (AIC) difference <2 and identical c-statistics, CPB was removed from model A to improve ease of bedside application.

Forward-backward stepwise variable selection based on the AIC was implemented separately on each candidate model. The accuracy and fit of the best model from each candidate model were assessed using the area under the receiver operating characteristic curve (AUC or c-statistic hereafter). The assessments were obtained by averaging across 100 random iterations of 10-fold cross validation. We also reported c-statistics obtained from predictions on external data set (not cross-validated). We approximated the 95% confidence intervals (CIs) for c-statistic using a normal distribution based on large sample theory.[26] Predictive model calibration was tested using the Hosmer-Lemeshow goodness of fit test. The odds ratios (ORs) and their 95% CIs from the logistic regression model predicting chylothorax are reported. We also report on the resulting specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), and accuracy after applying Youden's J-statistic to the predicted probabilities of chylothorax detection from our models. Statistical significance was assessed at the 0.05 level using two-tailed tests. Statistical analyses were implemented using R v. 3.6.0 (R Core Team, 2019).

External validation

External validation was performed using chylothorax patients < 18 years of age who underwent cardiac surgery at Lucile Packard Children's Hospital, a tertiary-care academic center in Palo Alto, CA, between March 2017 and May 2020. The inclusion and exclusion criteria and methods for chylothorax detection were the same as the development cohort. Each chylothorax patient was matched 1:2 based on gender and presence of genetic condition, as these variables were not selected in our chylothorax prediction models and were not otherwise associated with chylothorax. All had a measured CTO volume on PCD 1.

Results

A total of 735 patients with 763 encounters were analyzed after exclusion, of which 72 had chylothorax (Supplementary Fig. 1). Patients with chylothorax were younger, weighed less at the time of the index operation, underwent higher risk surgeries (STAT 4, 5 vs. STAT 1–3), had longer CPB times, had more DSC, and had higher CTO on PCD 1 (all $p < 0.001$) compared to encounters without chylothorax (Table 1). The frequency of genetic conditions was similar in both groups. Among those with DSC (14%, n = 106), median time to chest closure was 2 days (IQR 2, 3). The median time from chest closure to diagnosis of chylothorax was 3 days (IQR 3, 5).

Table 1
Demographics and Clinical Characteristics of Developmental Cohort

	Total (n = 763)	**No Chylothorax (n = 691)**	**Chylothorax (n = 72)**	**P-value**
Male[a]	437 (57%)	394 (57%)	43 (60%)	0.66
Genetic condition[a]	206 (27%)	185 (27%)	21 (29%)	0.66
Surgical weight (kg, median)	6.2 (IQR 3.6, 14.2)	6.4 (IQR 3.8, 14.9)	4.0 (IQR 3.1, 6.5)	**< 0.001**
Age at surgery (years, median)	0.5 (IQR 0.1, 3.4)	0.5 (IQR 0.1, 3.7)	0.2 (IQR 0, 0.5)	**< 0.001**
DSC	106 (14%)	79 (11%)	27 (38%)	**< 0.001**
CPB time (minutes, median)	100 (IQR 62.5, 136)	96 (IQR 60, 132)	133 (IQR 97, 160)	**< 0.001**
STAT category 1, 2, 3	443 (58%)	419 (61%)	24 (33%)	**< 0.001**
STAT category 4, 5	320 (42%)	272 (39%)	48 (67%)	
Prior cardiac surgeries	412 (54%)	372 (54%)	40 (55%)	0.96
PCD at chylothorax diagnosis (day, median)			3 (IQR 3, 5)	
CTO on PCD 1 (mL/kg/day, median)		6.9 (IQR 2.7, 13.6)	25.0 (IQR 16.5, 36.4)	**< 0.001**

[a] Matched variables in the cohort

[b] DSC – delayed sternal closure, CPB – cardiopulmonary bypass, PCD – post-closure day, CTO – chest tube output, STAT - The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery

Missing Values: None

Chylothorax encounters had a higher daily (PCD 1 through 10) mean CTO than non-chylothorax encounters (22.3 mL/kg/day vs. 5.2 mL/kg/day) (Fig. 1). As CTO on PCD 1 increased, the predicted probability of chylothorax increased exponentially (Fig. 2).

Univariable analysis of candidate predictors are shown in supplementary table 4. Odds of chylothorax increased with STAT category 4 and 5 surgeries, CPB time, DSC, and CTO on PCD 1 as a dichotomized and continuous variable.

Model performance

Model A selected CTO on PCD 1 dichotomized at 15.6 mL/kg/day (OR 11.3, 95% CI 6.3, 21.3, p < 0.001) and DSC (OR 1.9, 95% CI 1.1, 3.5, p < 0.029) (Table 2). The c-statistic was 0.78 (95% CI 0.73, 0.82). The sensitivity was 78% (95% CI 0.66, 0.87), specificity was 79% (95% CI 0.76, 0.82), positive predictive value was 28% (95% CI 0.25, 0.42), and negative predictive value was 97% (95% CI 0.95, 0.98).

Table 2
Early Detection of Chylothorax Multivariable Regression Models

Model A[a]				
	Odds Ratio (95% CI)	p-value	c-statistic[c]	AIC
CTO on PCD 1 ≥ 15.6 mL/kg/day	11.3 (6.3,21.3)	< 0.001	0.78 (0.73, 0.82)	383
DSC (yes)	1.9 (1.1,3.5)	0.029		
Model B[b]				
CTO on PCD 1 (mL/kg/day)	1.11 (1.08, 1.14)	< 0.001	0.84 (0.80, 0.87)	357
DSC (yes)	1.80 (0.95, 3.32)	0.07		
[a]The odds of developing chylothorax when CTO is zero without DSC is exp(intercept) = 0.03, where the intercept is − 3.6.				
[b]The odds of developing chylothorax when CTO is zero without DSC is exp(intercept) = 0.02, where the intercept is − 4.1.				
[c]c-statistic comes from 100 random iterations of 10-fold cross-validation to protect against over-optimism (due to over-fitting).				
CI – Confidence interval, CTO – chest tube output,				

Model B selected CTO on PCD 1 as a linear continuous variable (OR = 1.11, 95% CI 1.08, 1.14, p < 0.001) and DSC (OR 1.80 95% CI 0.95, 3.32, p = 0.07) (Table 2). The c-statistic was 0.84 (95% CI 0.80, 0.87) (Table 2). Model C which used CTO on PCD 1 as non-linear variable performed similar to Model B (c-statistic 0.84, 95% CI 0.80, 0.88, AIC 359).

Model D which excluded all classifications of CTO on PCD 1 retained delayed sternal closure, cardiopulmonary bypass, and weight with a c-statistic of 0.72 (95% CI 0.67, 0.77).

External validation

Models A and B were externally validated using 57 chylothorax and 114 non-chylothorax patients from Lucille Packard Children's Hospital. Compared to the development cohort, the external validation cohort had higher CTO on PCD 1 ($p < 0.001$), were older ($p = 0.026$), and were more non-Caucasian ($p < 0.001$) (Supplementary Table 2). The median days after surgery to diagnosis using pleural fluid testing was 9.7 days (IQR 4.7, 15.3).

External validation of Models A and B was good with c-statistics of 0.84 (95% CI: 0.78, 0.90) and 0.89 (95% CI: 0.84, 0.93) respectively. The Hosmer Lemeshow observed to expected goodness of fit plot shows good model calibration ($p = 0.36$ and $p = 0.71$ respectively) (Supplementary Fig. 2).

COMMENT

We report on novel and parsimonious predictive models for chylothorax in pediatric cardiac patients on the PCD 1. The models have good discrimination (c-statistic 0.78 and 0.84) with similar performance when externally validated (c-statistic 0.84). Our models demonstrate that volume of CTO on PCD 1 is an important variable in predicting the odds of chylothorax. The models we developed do not rely on delivery of enteral nutrition, which is a distinct advantage over using pleural fluid testing which is the current diagnostic standard.

Diagnostic levels of chylomicrons and triglycerides are dependent on a regular fat diet due to long-chain triglycerides being directly absorbed from the gut into the lymphatic system.[7, 8, 14] Some centers routinely diagnose chylothorax by clinical appearance of milky fluid. However, about 25% of chylothorax cases do not have the characteristic appearance, especially in fasting patients or those with genetic syndromes or abnormal lymphatic development.[7, 13, 14, 27] Illness severity is directly related to the likelihood that enteral nutrition is withheld. Thus, the most critically ill chylothorax patients may be at highest risk for delayed diagnosis when solely relying on traditional pleural fluid testing or qualitative assessment.

Patient surgical complexity and acuity are directly related to both chylothorax prevalence and associated morbidity.[14, 28, 29] Early chylothorax diagnosis in the postoperative period leads to early resolution, and conservative therapy such as afterload reduction, diuresis, and other measures to prevent venous hypertension or lymphatic obstruction may be more effective when used without delay. [1, 5, 8] For the sickest patients who do not receive enteral nutrition, our models could facilitate detection as early as the first day after sternal closure with more expeditious management when compared to diagnosis that occurred on the third and tenth days after sternal closure in the internal and external cohorts, respectively.

Similar to prior multivariate analysis, we also found a higher prevalence of chylothorax in patients with single ventricle and higher complexity surgeries, longer cardiopulmonary bypass (CPB) times, and younger surgical ages. [5, 23, 28]. However, these prior models did not include any measure of CTO

volume. The c-statistic improves from 0.72 to 0.84 when CTO on PCD 1 as a continuous variable is added to the model, demonstrating the importance of this novel covariate in predicting the odds of chylothorax.

We recognize that applying this model could result in some patients being unnecessarily treated for chylothorax. However, since incremental CTO increases chylothorax risk, we would use high CTO to stratify risk and guide confirmatory pleural fluid testing. The potential benefit of mitigating the adverse effects of chylothorax through earlier treatment and resolution would be weighed against the relatively low risk of noninvasive therapies such as fat-modified diet, diuretics, or milrinone, particularly if those therapies are short-lived. It is also possible that the hemodynamic significance of high chest tube output may be underappreciated, and that treatments to alleviate lymphatic or venous hypertension may be beneficial or even preclude chylothorax diagnosis. This analysis shows the potential value of a point-of-care predictive metric for chylothorax in pediatric cardiac intensive care units.

The literature suggests that protocolized management of chylothorax reduces time to diagnosis, treatment duration and time without feeds, chest tube and central line utilization, duration of mechanical ventilation and length of ICU and hospital stay.[1, 3, 30, 31] Incorporation of our model in protocols to trigger pleural fluid testing irrespective of milky appearing pleural fluid could allow for earlier detection and potentially earlier treatment and resolution. We look to incorporate inflammatory and immune mediated biomarkers into future iterations, investigate the influence of physiologic risk profiles including fluid balance, central venous pressures and postoperative pulmonary hypertension on model discrimination.

Limitations include those inherent to retrospective analyses, which were used for both model development and external validation. Additionally, there is potentially a confounder effect due to unknown covariates with incompletely understood pathophysiology of chylothorax and covariates reported in other studies that we did not collect such as thrombosis data, central line use, hemodynamic and nutritional data, or specific cardiac lesions. Given the variable incidence of chylothorax across centers it is also plausible that the etiology may also vary and thus high CTO may not be an early manifestation at other centers.[1, 3, 4, 7, 8, 11, 14, 21, 28, 32, 33] However, our external validation results suggest the model is generalizable.

High volume chest tube output on the first day after sternal closure may predict chylothorax earlier than traditional diagnosis by pleural fluid testing, independent of enteral nutrition. Early detection and treatment can potentially decrease time to resolution, which may have the greatest impact on the most critically ill patients who are not fed enterally.

Abbreviations

AIC	Akaike Information Criteria
AUC	Area under the receiver operating characteristic curve
CI	Confidence interval
CPB	Cardiopulmonary bypass
CTO	Chest tube output
DSC	Delayed sternal closure
IQR	Interquartile range
LOS	Length of stay
NPV	Negative predictive value
OR	Odds ratio
PCD	Post-closure day
PPV	Positive predictive value
STAT	Society of Thoracic Surgeons—European Association for Cardio-Thoracic Surgery

Declarations

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Figures

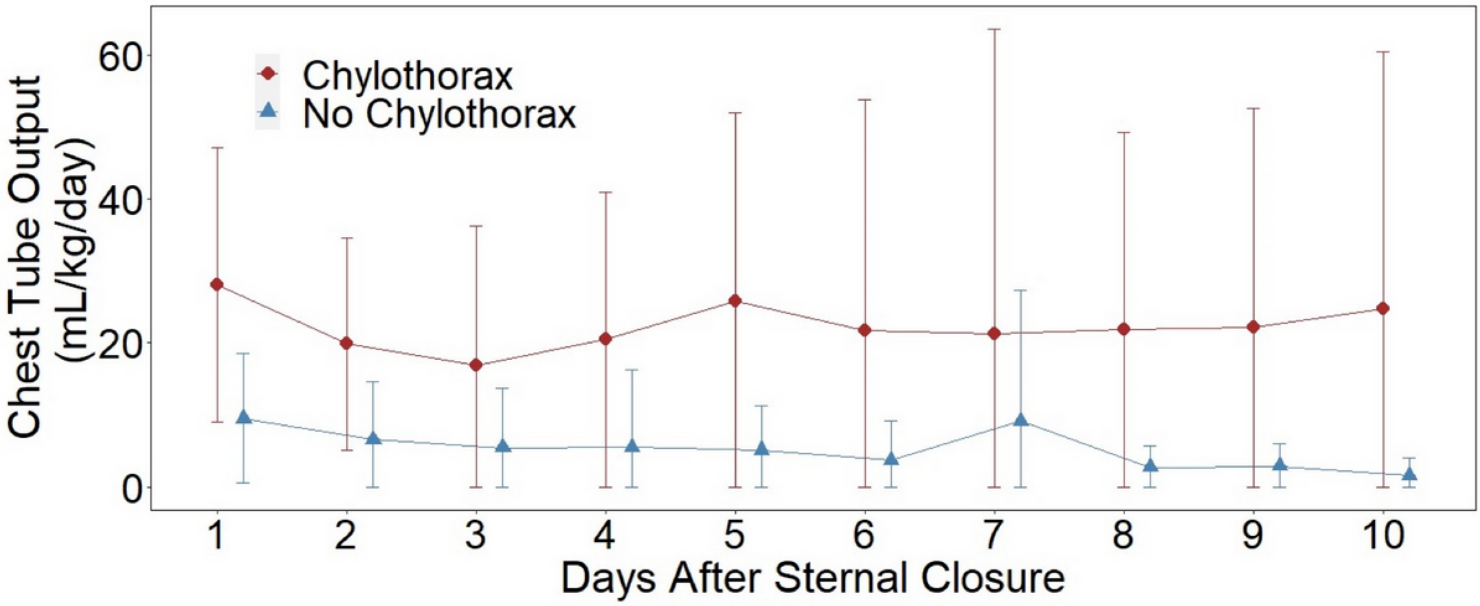

Figure 1

Average Daily Chest Tube Output With and Without Chylothorax in Developmental Cohort (error bars +/- one standard deviation)

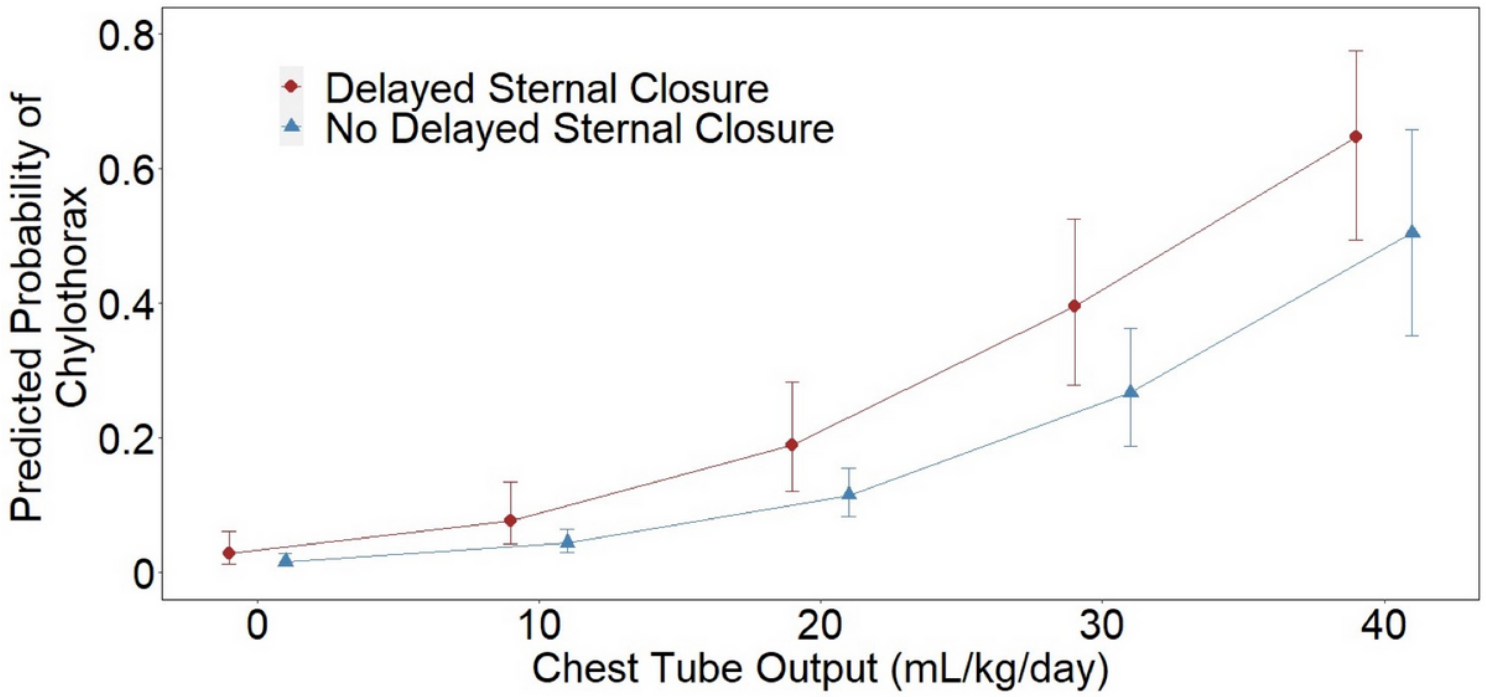

Figure 2

Predicted Probability of Chylothorax Based on Volume of Chest Tube Output

Supplementary Files

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- SupplementalAppendixMaterial.docx
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- SupplementaryFigure2.jpeg
- SupplementaryFigure3.jpeg