Peer Review File
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Reviewer A

Abstract	
C1	Conclusion should be an interpretation of the results, instead of restating the results.
R1	We have modified the conclusion part of the abstract as "Conclusions: Most (89.2%) cases of chylothorax were successfully treated conservatively using dietary modification and octreotide therapy. The effective dietary modification to avoid parenteral nutrition accompanied with protocolized treatment are crucial to improve the overall outcomes. "
	Change in text: see page 3, line 16-20.
Introduction:	
C2	-The sentence beginning on line 7 should be adjusted to read "…treatment of chylothorax is eliminating long-chain triglycerides from the diet…" as other forms of fat (MCT) are acceptable as they are not absorbed into the lymphatic system from the gut.
R2	We have modified the text as advised as "…Since chyle represents the lymph from the gastrointestinal system, the principal treatment of chylothorax is eliminating long-chain triglycerides from the diet to decrease the flow of chyle…"
	Change in text: see Page 4, line 7-9
C3	-The sentence beginning on line 13 (However, the pediatric population…) is unclear. How does age-specific dietary needs make them more vulnerable to malnutrition? The following sentence (Dietary modification…) is unnecessary.
R3	Age-specific dietary in newborns is directly related to obtaining nutrition from milk either from the mother or formula feeding, and these are considered fat-enriched diets. We have now revised the sentence for more clarity. "…However, neonates and young infants are milk consumers; both human and formula milk are fat-enriched diet…."
	Change in text : see Page 4, line 14-15
C4	-Second paragraph – first sentence makes it sound like the protocols lead to complications related to treatment modalities. Maybe this should be two sentences, one about how protocols lead to a wide variety in practice and a second that discusses the variation in outcomes and complications due to the complex and varied nature of chylothorax in children.
R4	We have modified our text as advised as "…..Since there are various treatment options to manage chylothorax, variation among these methods may affect outcomes and complications. ……"

	Change in text: see Page 4, line 20-21
Methods	
C5	-Are these patients diagnosed with chylothorax across all service line? Neonatal ICU, Cardiac ICU, floor wards, etc?
R5	Yes, our study included all pediatric patients diagnosed with chylothorax from our institute across all service lines, including neonatal ICU, pediatric ICU (serving for all medically-ill, traumatic, surgical, and cardiac surgery patients), general pediatric, and pediatric surgical ward. We have revised the text as "…… across all pediatrics service lines in Songklanagarind Hospital in southern Thailand"
	Chang in text: see Page 5 ,line 9-10
C6	Were treatment strategies different based on etiology? For example, was thoracic duct ligation avoided in patients with congenital chylothorax?
R6	No, the treatment practice for chylothorax in this study started with dietary modification (with various types of diets and protocols) with or without octreotide treatment for all cases independently of the etiology of chylothorax. Surgical correction for chylothorax, which was thoracic duct ligation with or without pleurodesis, was considered when patients underwent unsuccessful conservative treatment.
	No change in text.
C7	Were diet changes utilized beyond resolution?
R7	Yes, some patients continued to receive the fat-modified diet beyond the point of resolution based on either physician's prescription or patient's preference. It was not appropriate to consider this as a treatment. Hence, we decided not to include dietary modification beyond point of resolution as treatments. We have made this point in the revised text "…Dietary modification after the resolution point was not counted as chylothorax treatment".
	Change in text : see page 6, line 3-4
Results	
C8	-PDA ligations is an interesting operation to encompass 21% of chylothorax patients. Were these PDA ligations isolated repairs? Through lateral thoracotomy?
R8	Yes, PDA ligation operation means isolated procedure for PDA ligation or repaired. It was performed through lateral thoracotomy in all cases. We have added text to highlight this: "isolated patent ductus arteriosus repair (21.2%),…" AND in table 1 (column 1 row 6) as "Isolated PDA repair or ligation"
	Change in text: see Page 8, line 7 AND table 1 (column 1 row 6)
C9	-Please describe etiology of the 7 other patients (currently understand 52 to be surgical and 6 to be congenital).
R9	The etiologies of other seven patients chylothorax were malignant related in five patients and spontaneous/idiopathic in 2 patients. The data are summarized in Table 1. We have also added text as. "Other remaining seven cases of chylothorax

	were malignant-related and spontaneous (Table 1)"
	Change in text ; see Page 8,line 10-11
C10	- Page 7, line 21 – are new chest tubes inserted after chylothorax diagnosis in all patients? This is what this sentence leads me to believe. Please describe if this is the case, as typically existing chest tubes are adequate for drainage of chylothorax.
R10	All chylothorax cases were drained by a chest tube either inserted immediately after diagnosis or via a pre-existing chest tube (if it was still functioning). We added text as "……All episodes of chylothorax were drained by a chest tube (either newly inserted or continued use the preexisting chest tube especially in postoperative cases)."
	Change in text: Page 8, line 20-21
C11	Page 8, line 1 – is this dietary modification referring only to initial treatment? Or did only 51% ever have a dietary modification? Table 3 shows "diet" changes as a treatment option for all but 9 patients (fasting + TPN), which is also interesting…did these 9 patients only have NPO days and never had a diet change?
R11	Dietary modification is shown in Table 2. It refers to all courses of treatment for each patients, and not just the initial treatment. - 50.8% received dietary modification without medication or surgery; "stepwise diet" means dietary modification performed stepwise to escalate fat consumption e.g., start with fasting with fat-free diet and then escalate to low-fat diet until finally moved to full-fat diet. -Nine patients received fasting+TPN treatment only for all courses of their chylothorax treatment; all of them were neonates who were prescribed TPN for a while till chylothorax resolved and then normal formula milk was resumed. We have made following text changes: 1) In methods section: "…. 1) dietary modification: fasting with TPN, FF, LF, or MCT-enriched diet. These were usually prescribed in stepwise manner, beginning with the most intense restriction on enteral fats either via fasting with TPN or FF diet. Gradually, long-chain triglycerides (MCT-enriched or LF diet) were started." 2) In result section: …. Nine neonates received fasting with TPN treatment until chylothorax resolved" 3) Change text in table 2 (column 1 in left side, row 2) stepwise diet to " dietary modification"
	Change in text: see page 6 line 6-10, AND page 9,line 2-4 AND Table 2 (column 1 in left side , row 2)
C12	Removal of chest tubes is considered the point of resolution…can you please report chest tube days or days to resolution in the results? Tables 2 and 3 have "treatment duration" – is this days to resolution or the days that any treatment was in place?

R12	Chest tube days or days to resolution refer to the treatment duration itself because treatment duration was defined as the time between **chylothorax diagnosis** (most patient had a chest tube inserted on this day, except some postoperative patients who had a pre-existing chest tube, immediately postoperatively) to **chyothorax resolution,** which means the day of chest tube removal; hence, we believe that chest tube day is similar to treatment duration. We add some text as "The treatment duration was defined as the time between chylothorax was diagnosed to the resolution point"
	Change in text : Page 6, line 2-3
C13	Page 9, line 3, please describe the cause of the other 4 deaths.
R13	There were eight in-hospital deaths in our study, two of whom died before chylothorax resolution (as described previously in text). The other six patients had completely resolved chylothorax but did not survive to discharge because four had sepsis, one had hypoxic arrest from accidental extubation, and one had congenital heart defect with cardiogenic shock. We added some text as "The other six patients, although had chylothorax completely resolved, did not survive; four had sepsis, one had hypoxic arrest, and one had congenital heart defect with cardiogenic shock."
	Change in text: see Page 10 line 10-12
C14	-Page 9, line 6 – what outcomes are considered morbidities? Are these the complications listed in Table 3? This needs to be more clearly described as describing complications is one of the main aims of the paper. Describing these complications is where this paper adds novel information to the available literature, so this should be more of a focus.
R14	Yes, morbidities meant having any complication during chylothorax treatment. We already added the definition of each complication in the Methods section, We added text as "The data from mortality and morbidity occurring during treatment for chylothorax were collected .The patient's morbidities occurred after chylothorax included sepsis, hypoalbuminemia (serum albumin <3.5 g/dL), ventilator-associated pneumonia (pneumonia diagnosed in intubated-patients with prolonged ventilator use >48 h or patients within 48 h after extubation), hospital-acquired pneumonia (pneumonia diagnosed after >48 h hospitalization), ICD-related complications (consists of pneumothorax, pleural infection, chest tube wound infection), TPN-related metabolic disturbances (significant electrolyte abnormalities which required medical intervention during TPN administration), TPN-related liver diseases (elevation of liver enzyme and/or alkaline phosphatase 1.5-3 times the upper limit of normal values within 1-3 weeks of initiation of TPN), catheter-related complications (consists of catheter-related blood stream infection, catheter exit site infection, displacement and significant leakage or malfunction of catheter, which required removal/replacement)."

	Change in text: see page 6 line 18-23, page 7 line1-5
C15	-Page 9, line 10 – please describe ICD-related complications (in methods). Also define the other complications listed in Table 3. If I wanted to compare these outcomes to those at my own institution, I would be unable to tell if we defined these complications in the same way.
R15	We have added definition of each complication in the Methods section.
	Change in text: see page 6 line 18-23, page 7 line1-5
C16	-Why was clot not included as a complication?
R16	If the clot is an intravascular clot or thrombosis, we do not routinely perform Doppler ultrasonography for definite diagnosis of venous thrombosis except in patients with clinical symptoms indicating suspected deep vein thrombosis. There was no patient in our report with definite thrombosis diagnosis. However, some patients with an existing catheter might have a clot/thrombosis and present with catheter occlusion/malfunction, which we considered catheter-related complications. We added text as: "…. catheter-related complications (consists of catheter-related blood stream infection, catheter exit site infection, displacement and significant leakage or malfunction of catheter, which required removal/replacement)."
	Change in text: see Page 7 line 3-5
C17	-The complications listed as "related to chylothorax" should be described in a different way. The majority of these issues can also have causes unrelated to chylothorax (lung disease, immunocompromise, respiratory infection, etc.). The patient may be at higher risk because of chylothorax but there is no proof they are directly related.
R17	We agree that few events may have also occurred unrelated to chylothorax e.g., sepsis or pneumonia. We have re-formatted and changed some text in Table 3. We described the complications that occurred in patients during chylothorax treatment as "complication during treatment."
	Change in text: Table 3
C18	-Table 4 – how were variables chosen for the logistic regression model? Are only significant variables shown? If not, why were other complications not analyzed? How many patients had a hospital stay >28 days?
R18	A total of 34 patients died before discharge (in-hospital death) or had hospital stay >28 days. In-hospital death or hospitalization >28 days were considered unfavorable outcomes in our study. We selected significant variables ($P<0.05$) in logistic regression. Table 4 has been changed and re-formatted to explain these issues. Revised text: "The in-hospital death and prolonged hospitalization (>28 days) were considered as unfavorable treatment outcome. ……. Data were analyzed …… For the exploratory analysis,

	multivariable logistic regression with significant factors for unfavorable treatment outcome (P <0.05) in univariate was used. The collinearity was assessed, and the model was sequentially reduced by eliminating non-significant predictors, yielding the final reduced model. The results are reported as adjusted odds ratios (aOR) with their 95% confidence intervals (CIs)."
	Change in text: page 7 line 7-8, line 15-19 AND table 4
	Discussion:
C19	-Page 10 paragraph 1 – Do you feel there is an advantage to thoracic duct ligation? Many are moving to less invasive strategies such as thoracic duct embolization. Do you have the capability to do lymphatic imaging at your institution? If not, it would be more interesting to describe your outcomes as a center without those options and how your outcomes relate to others.
R19	At our institute, performing lymphatic imaging is difficult and thoracic duct embolization is not available. Revised text: "…..Although most of chylothorax episodes (89%) were successfully treated with conservative methods, the rate of thoracic duct ligation in our study (10.8%) was slightly higher than that in most recent studies (4-9%) (6-9,13). There is less variety of therapeutic options at our institute. The use of many non-surgical interventions reported in postoperative chylothorax, were hardly observed in our study including steroids, propranolol, chemical pleurodesis, and intravenous immunoglobulin (4,6,8,9,14,15). Further, the thoracic duct embolization, which was identified as another effective, less-invasive option for chylothorax in recent years (9,16,17), is not available at our institute.
	Change in text: page 11, line 18-23 and page 12, line 1-2
C20	In patients with thoracic duct ligation, how long from the surgery until resolution? Were there surgical complications? Chyloperitoneum? If not, this could be presented as a viable option in centers not performing lymphatic imaging/interventions.
R20	The median time to chylothorax resolution after lymphatic duct ligation (N=7) was 11 days (IQR 8-30) with no postoperative complications. Revised text: "All operations were able to resolve chyle leakage with a median time of 11 days (IQR 8-30) after surgery. None of the patients had postoperative complications.
	Change in text: see Page 10 line 3-4
C21	-Page 10 paragraph 2 – I'm still very confused as to how the data is presented in regards to TPN and diet. The tables show only 9 with TPN – is this only those that solely use TPN but it could've been used in others? Where does 87.7% come from? The only percentage related to TPN I see is 13.8% in the table. The discussion should not be the first place a result is reported.
	Table 2 shows the data of nine patients treated with fasting+TPN, suggesting

	that these patients received only TPN treatment., no more other fat-modified diet. Others in tables which have "diet" as composition of treatment may be also receive fasting+TPN along with other type of dietary modification eg. TPN + low fat diet or fat free diet Revised text: "….Overall TPN prescription rate was 87.7% of all episodes, with median duration of TPN use of 14 days (IQR 9-25)"
	Change in text: Page 9 line 3-4
C22	-"Stepwise dietary modification" should be initially defined in methods, not in the discussion for the first time. What causes you to step "back and forth" – chest tube output? How is this accomplished in formula fed patients?
R22	Stepwise dietary modification indicated the escalation and de-escalation of long-chain fat density in patient's diet based on the amount of daily chyle leakage (which equals to daily chest tube output). In patients with formula feeding, we limited the choice of fat-modified formula. Hence, the stepwise dietary in these patients began with fasting+TPN and gradually the MCT-rich formula was introduced while gradually decreasing the amount of parenteral nutrition until patient can tolerate full enteral feeding with the MCT-rich formula without increased chyle leakage. Finally, we substituted the MCT-rich formula with normal formula. Revised text in the Methods section as follows: " .. 1) dietary modification: fasting with TPN or FF diet or LF diet or MCT-enriched diet. It usually prescribed in stepwise manner which begin with the most intensity of enteral fat restriction either fasting with TPN or FF diet. Then gradually escalation of long-chain triglyceride composition in patient's diet as MCT-enriched diet or LF." Table 2 changes: from "stepwise diet" to "dietary modification" for consistency
	Change in text: Page 6 line 6-10 AND Table 2
C23	-Page 10 line 20 – you cannot show that TPN is "responsible" for increased catheter-related complications, but that younger age is associated with increased risk.
R23	We agree to this point and revised text: "… Further, newborns were associated with increased risk of complications, including catheter-related complications.
	Change in text: Page 12 line 21-22
C24	-Page 11 – do you offer defatted or LF human milk at your institution? I'm also still wondering if "treatment duration" includes the entire length of using MCT formulas.
R24	We did not have access to modified human milk both defatted or LF. The treatment duration in our study indicated the duration between chylothorax diagnosis to resolution, Resolution was considered to be achieved when the

	chest tube was successfully removed. MCT formula was continued in few patients after removal of chest tube, but we could not include it as a "treatment" because it is difficult to identify the effect of this intervention on the outcomes (chyle volume or chest tube volume). Revised text: "…..Removal of the chest tube drain was considered the resolution point of chylothorax .The treatment duration was defined as the time between chylothorax was diagnosed to the resolution point. Dietary modification after the resolution point was not counted as chylothorax treatment.".
	Change in text : Page 6 line 1-4
C25	-Page 11 paragraph 2 – With over double the number of patients treated with octreotide yet no change in treatment duration, hospitalization or morbidity or mortality rates, can you comment on the fact that maybe octreotide isn't actually effective? Or do you think the patient population changed enough to account for worse chylothorax that was effectively treated with octreotide? The most common reason that octreotide is discredited is that it is started late and the resolution rate may actually follow what would have happened regardless of octreotide.
R25	We cannot conclude that octreotide might be ineffective in our study because of variation in drug initiation and dosage titration. Revised text: " … The efficacy of octreotide in this study could not be determined since there was no specific protocol, and octreotides were initiated in different stage of chylothorax."
	Change in text: see Page 13 line 21-23
C26	Page 11 line 19 – should be these morbidities which "may be consequences…"
R26	Revised text: "…Other morbidities observed during chylothorax treatment in our study, including sepsis and hypoalbuminemia, were possibly the result of prolonged chyle loss …"
	Change in text: see page 14 line 8-10.
C27	-The discussion definitely misses the opportunity to comment more on the common complications related to chylothorax and treatment. Each of the significant variables in the multivariable model should be discussed. Have these factors been noted elsewhere in the literature? What else was adjusted for? Could other factors have influenced the outcomes.
R27	Added text in the Discussion section to address all the points you raised in this comment: "… The mechanical ventilation requirement and ventilator-associated pneumonia were observed more in younger patients (age <1 years). This may not be the consequence of chylothorax alone and may also influenced by cardiopulmonary compromise of infants especially after post-cardiac surgery. The recent systematic analysis of congenital chylothorax of newborns (27)

	also reported a high rate of mechanical ventilator use (56%), similar to our study. Other morbidities observed during chylothorax treatment in our study, including sepsis and hypoalbuminemia, were possibly the result of prolonged chyle loss, while few may be related to TPN administration, ICD, and catheter placement. These factors have not been emphasized in previous studies in children (5-9). Non-operative chylothorax is one of the significant risk factors related to unfavorable outcomes, which has also been reported in previous study in adult patients (28). The potential modifiable risk factors are the use of TPN >14 days and hypoalbuminemia. With in-depth exploration, we also found that the initial prolonged fasting (>7 days) as an aggressive fat restriction strategy does not significantly decrease the length of treatment duration and hospitalization. This emphasizes the benefit of fat-modified diet as early as possible. Furthermore, the elimination of enteral feeding for chylothorax treatment should be discouraged.”
	Change in text : see Page 14, line 4-18
C28	-There is no limitations section. Please add.
R28	We added new paragraph in Discussion section for limitation of the study. Revised text: “This study was a retrospective study conducted over 20 years period, and hence, the treatment strategies were depended on the physician’s practice preference and resource availability. The effectiveness of such modalities and outcomes should be interpreted with caution.”
	Change in text: see page 14 line 20-22
C29	-The conclusion should be more of a summary instead of directly restating results. Also, there are unique neonatal/infant formulas for dietary management of chylothorax (Enfaport, Monogen, Vivonex…), so the last sentence is confusing.
R 29	We revised the Conclusion paragraph according to your comment. As “…In our study, most (89.2%) of chylothorax were successfully treated conservatively, using dietary modification and octreotide therapy. Uneven treatment protocol resulted in difficulty to define the effectiveness of each therapeutic option. Young children aged <1 year were challenging patients due to limitations of appropriate nutritional options and higher risk for specific complications. The effective dietary modification to avoid parenteral nutrition accompanied with protocolized treatment are crucial to improve the overall outcomes.”
	Change in text: see page 15 line 1-7

Reviewer B

C30	- Page 8, line 11: What do authors mean by successful treatment with octreotide? Can you define it? At what point was it called treatment failure and surgery was considered?
	Octreotide failure in our study was defined as cases in which patients received octreotide for chylothorax treatment and underwent surgical correction for chylothorax after octreotide initiation. However, guidelines on confirming octreotide failure are not established at our institute, and physicians usually make a decision on persistent or progressive leakage after prolong octreotide treatment (generally >7 days). Revised text: "….The failure of conservative treatment was defined as cases wherein surgical corrections were required after dietary modifications or octreotide administration."
	Change in text: Page 6 line 13-15.
C31	- Page 8, line 21: Post op, how many days did it take for chylothorax resolution? Did it resolve immediately post op or in a couple of days/weeks?
	The median time to chylothorax resolution after lymphatic duct ligation (N=7) was 11 days (IQR 8-30) with no postoperative complications. Revised text: "All operations were able to resolve chyle leakage with a median time of 11 days (IQR 8-30) after surgery. None of the patients had postoperative complications."
	Change in text: see Page 10 line 14-16
C32	- Page 9, line 2: There were 8 deaths. Apart from the 2 causes of death mentioned- sepsis and congenital anomalies, what were the other causes of death? Were any of these deaths related to chylothorax or its treatment?
	There were 8 in-hospital deaths in our study, 2 of whom died before chylothorax resolution (as described previously in text). The other 6 patients had completely resolved chylothorax but did not survive to discharge because 4 had sepsis, 1 had hypoxic arrest from accidental extubation, and 1 had congenital heart defect with cardiogenic shock. Some deaths were not related to chylothorax such as hypoxic arrest from accidental extubation. However, the relation of death from sepsis either during or after chylothorax resolution with chylothorax or its treatment or other patient's illness is difficult to determine. Revised text: "….The other six patients, although had chylothorax completely resolved, did not survive; four had sepsis, one had hypoxic arrest, and one had congenital heart defect with cardiogenic shock."
	Change in text: see Page 10 line 10-12