

Peer Review File

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Reviewer A

Comment 1: Not clear query criteria

Reply 1: We are unsure what is being referred to explicitly by this comment. However, we have interpreted this as relating to the need for slight clarification of the diagnostic criteria that was presented in the abstract, akin to the comment by Reviewer C below. We have adjusted the relevant description in the abstract (p.2) and conclusion (p.15) to clarify this point, as well as updating Table 2 to make the diagnostic criteria for chylothorax less ambiguous.

Comment 2: Any take home message in clinical Practice

Reply 2: Thank you for this suggestion. We have now included a box highlighting 'key points for clinical practice' which provides some take home messages for the reader.

Reviewer B

Comment 1: I do not find myself contraindicating anything in particular other than reporting further attempts at pleuridesis to be added to the methods listed in line 417: J Cardiothorac Surg 2021 Zhang K "Treatment of chylothorax complicating pulmonary resection with Hypertonic glucose Pleurdesis".

Reply 1: We thank the reviewer for this comment, and have now included this as an additional method of pleurodesis reported with the associated reference.

Comment 2: In the surgical methods it is possible to underline some techniques for identifying the duct lesion such as: "Preoperative red sudan administration to locate thoracic duct lesion in videothoracoscopy" Eur J Cardiothorac Surg 2007 Divisi D.

Reply 2: Thank you for this suggestion. We have included an additional sentence in the relevant section on surgical techniques (p.15), highlighting that various pre-operative dye agents can be utilized to aid accurate identification of the thoracic duct defect (including appropriate references).

Reviewer C

Major issues:

Comment 1: Line 45. Suggest removing “imaging” as imaging itself doesn’t help with the diagnosis of chylothorax, though it is important to find out the underlying cause and identify the site of leak, which you have addressed between lines 47 and 49.

Reply 1: Thank you for this comment. We agree that imaging in itself does not confirm the diagnosis of chylothorax, but rather may help to establish the likely underlying cause and site of chyle leak, as we subsequently state. We have now removed the word ‘imaging’ from the relevant sentence in the abstract and updated this statement accordingly (p.2).

Comment 2: Line 47. The linkage between “chylomicron as the definitive criterion” and “most diagnoses by pleural fluid triglyceride and cholesterol levels” is unclear here. It would make readers confused why the chylomicron test is not used commonly.

Reply 2: We apologize for any confusion regarding the criterion for diagnosis of chylothorax within the abstract. We have now adjusted these two sentences (p.2) to emphasize that, in clinical practice, the most widely accepted diagnostic criteria is demonstration of elevated triglyceride levels and reduced cholesterol levels. We describe in the text, and also highlight in the new clinical practice points box, that while demonstration of chylomicrons is definitive for the diagnosis of chylothorax, this test is not routinely performed in practice (but may be employed in cases where the diagnosis remains uncertain). We have also updated Table 2 to provide a clearer summary of the diagnostic criteria used in the diagnosis of chylothorax.

Comment 3: Consider adding a short sentence in the abstract session, stating that “insufficient high-quality evidence” in advising the management for chylothorax, and that’s why there is no standardized guideline (line 57).

Reply 3: Thank you for this suggestion. We have adjusted the final sentence of the abstract (p.2) to incorporate the message that there is a paucity of high-quality evidence, as well as standardized guidelines, in supporting the management of chylothorax, which must therefore be patient-centered and guided by multi-disciplinary discussion.

Comment 4: Consider adding a session discussing outcomes of chylothorax before the conclusion, instead of a few sentences about mortality in the introduction session.

Reply 4: We thank the reviewer for this suggestion. We do feel that it is important to provide some context within the introduction relating to mortality associated with chylothorax, given this is not insubstantial and underpins many of the management decisions that are subsequently discussed within the review. However, we accept that the inclusion of a short section relating to chylothorax outcomes, prior to the conclusion, may be helpful for the reader – we have therefore included this within the revised manuscript (p17).

Comment 5: Line 72. Consider adding “judicious drainage of pleural effusion” after “appropriate interventions”.

Reply 5: Thank you for this suggestion – we have included this statement within the relevant sentence of the introduction (p.3).

Comment 6: The authors had cited “Phang K, Bowman M, Phillips A, Windsor J. Review of thoracic duct anatomical variations and clinical implications. Clin Anat. 2014 May;27(4):637-44” (Ref 13), which stated that the most common site of termination is at the internal jugular vein (46%), followed by the jugulosubclavian angle (32%). This should be considered the most updated data (as the authors have summarized the evidence in the past 100 years) (line 86).

Reply 6: Thank you for this comment. We have added a sentence (p.3) to clarify the most common sites of termination of the thoracic duct with this reference.

Comment 7: Line 90. Bilateral chylothoraces happen when injury of the thoracic duct at the thoracic plane (Line 90)

Reply 7: We have adjusted the relevant sentence to clarify this point (p.4).

Comment 8: It would be preferable to briefly describe the source, component and physiological role of the chyle after describing the anatomy of the thoracic duct. This can help the readers to understand the different clinical outcomes and management of chylothorax

Reply 8: Thank you for this suggestion. We have included a short section ('Overview of chyle' (p.4) to address this.

Comment 9: Lines 123-126. I am not certain why the authors put a special remark on sarcoidosis here, as it is not the most common cause of non-traumatic chylothorax, and there is no detailed description of this in the remaining text.

Reply 9: Thank you for this comment. We agree that this particular statement on sarcoidosis does not hold much relevance to the rest of the manuscript – we have therefore removed it.

Comment 10: Lines 144 to 146. I suspect these causes, other than post-RT, are quite rare as only reported as isolated cases. The authors may consider saying that these conditions may rarely cause chylothorax or similar wordings

Reply 10: We thank the reviewer for this comment. We have adjusted the relevant sentence (p.5) to emphasise that these are less common causes of chylothorax.

Comment 11: Line 171, serous appearance may be possible if the patient is on (prolonged) fasting in the post-operative setting. In addition, chylothorax should be considered in pleural effusion with ongoing output but unknown causes.

Reply 11: Thank you for this comment. We fully agree with this point, and have made specific mention of the fact that chylothorax can occasionally present as serous fluid accumulation (see section on Pleural fluid analysis, p.7), particularly if patients are fasting. We have made a slight adjustment to the relevant sentence to emphasise that this could arise in the post-operative setting, as suggested.

We have now included a new clinical box with key take home messages for our readers, where we have emphasized the point that chylothorax should be considered in cases of pleural effusion with ongoing output of uncertain cause.

Comment 12: Line 207 to 208, the description could not clearly explain how we can distinguish chylothorax and pleural infection (it is more typical to see a separation of fluid components in empyema only) by centrifugation. For example, “Pleural fluid centrifugation can help to distinguish chylothorax and empyema with a milky appearance, with separation of the constituent fluid components / cell debris and clear supernatant in the latter condition”.

Reply 12: Thank you for this comment and recommended re-wording. We have adjusted the relevant sentence in line with this suggestion to aid clarity in the text (p.8).

Comment 13: Line 219. The presence of cholesterol crystal in the pleural fluid is also considered confirmatory for pseudochylothorax.

Reply 13: We thank the reviewer for this comment. We have adjusted the relevant sentence (p.8) to incorporate the presence of cholesterol crystals as an indication of pseudochylothorax diagnosis, which is also now emphasized in Table 2 (summary of diagnostic criteria).

Comment 14: Line 228. Dual pathology, especially transudative cause plus chylothorax, can lower the pleural fluid triglyceride (Respirol Case Rep. 2022 Mar; 10(3): e0907). In such case (cirrhotic effusion with atypical features), check for chylomicron can provide additional diagnostic evidence.

Reply 14: We thank the reviewer for this comment, and agree that it is important to

mention that dual pathology may impact the pleural fluid analysis, particularly relating to triglyceride levels. We have adjusted the relevant sentences (p.8) to incorporate the above suggestion, including the suggested reference.

Comment 15: Line 229. Such pleural fluid to serum TG ratio is important when the patients have high serum triglyceride levels or in rare situations when pseudochylothorax has a high TG level together with a high cholesterol level. That's why in line 216, a chylothorax can only be confirmed when fluid TG is high AND fluid cholesterol is low.

Reply 15: Thank you for this comment. We agree it is important to clarify the value of using the ratio of pleural fluid to serum triglyceride levels, and have subsequently adjusted the relevant sentence (p.9) to incorporate the suggested points highlighted here.

Comment 16: Line 275. The technique of dynamic contrast-enhanced magnetic resonance lymphangiography should also be discussed: Chavhan GB, Lam CZ, Greer MC, Temple M, Amaral J, Grosse-Wortmann L. Magnetic Resonance Lymphangiography. Radiol Clin North Am. 2020 Jul;58(4):693-706.

Reply 16: Thank you for this comment. We have now included mention of this technique within the relevant discussion on p.10 ('imaging' section).

Comment 17: Line 299, also to factor "rate of chyle leak" in consideration of the management plan

Reply 17: Thank you for this suggestion – we agree that the rate of chyle leak is also important to mention here and have adjusted the sentence accordingly (p.11).

Comment 18: Line 470, the authors may need to explain why abdominal aortic aneurysm is a contraindication. Is it because the procedure follows a transabdominal approach?

Reply 18: Thank you for this comment – the contraindication of AAA relates to the

necessity to traverse the abdomen to the retroperitoneum. We have clarified this statement in the revised document (p.16).

Comment 19: Line 471 and 472, are these complications common? Any incidence rate?

Reply 19: We thank the reviewer for this comment. The exact rates of complication for each of the individually listed complications is difficult to quantify, since existing data on these is limited. However, we have updated the relevant section (p.16) to include details on pooled complication rates for the procedure available from meta-analysis data.

Comment 20: Figure 1, the positions of arrows 1, 2 and 4 are misleading, as these pathogenic mechanisms can happen at all levels of the thoracic duct. The current position may confuse the readers that they are site-specific.

Reply 20: We thank the reviewer for this comment, and agree that the current position of arrows may be confusing. We have adjusted the Figure (now named Figure 2) accordingly to make these pathophysiological mechanisms clearer, including a more detailed description within the Figure legend to emphasise that the relevant mechanisms can occur at any level of the thoracic duct.

Comment 21: Figure 2, should a “*” also be put in the box “yes” following the box “Is the malignancy treatable?”.

Reply 21: We apologise for this error. We have now made some changes to this Figure (now named Figure 3), based on comments from Reviewer F, to make our suggested management algorithm less ambiguous and more succinct. As part of this, we have removed the “*” from the relevant box.

Comment 22: Table 1. Congenital chylothorax is not described in the text, please either mention it in the text briefly or remove it from the table.

Reply 22: We apologise for this oversight. We have now included specific mention of congenital chylothorax as a potential aetiology within the main text (see p.5, within

pathophysiology section); we also comment on this condition briefly in the section on pharmacological therapies (p. 13).

Comment 23: Table 1. Consider sorting the conditions causing secondary lymphatic dysfunction according to their frequency (a rough estimation as there are no known incidence rates).

Reply 23: We thank the reviewer for this suggestion. The exact incidence of secondary causes of lymphatic dysfunction are not clear, given the paucity of available literature that is largely based on single case reports. All are thought to be rare. However, it is generally accepted that radiotherapy is likely more commonly encountered than the other causes listed in the table. We have therefore adjusted the relevant section of the table to sort the conditions causing chylothorax 'Rarely' or 'Very rarely'.

Comment 24: Table 2. Consider constructing the table into 3 columns (with the first one belonging to the diagnostic criteria), this can make it more friendly to the readers.

Reply 24: Thank you for this suggestion. Table 2 has now been modified to incorporate a third column containing 'diagnostic criteria' to make this table more reader-friendly.

Comment 25: Table 2. Please also add a row stating that the presence of chylomicron and cholesterol crystal is confirmatory for chylothorax and pseudochylothorax respectively; another row on the appearance.

Reply 25: We thank the reviewer for this suggestion. We have added some additional rows to Table 2 to incorporate this information.

Minor issues:

Comment 1: Line 38. Consider adding "relevant" before "anatomy".

Reply 1: The word 'relevant' has now been included here, as well as in the separate section heading on p.3.

Comment 2: Line 45. Suggest removing "imaging" as imaging itself doesn't help with

the diagnosis of chylothorax, though it is important to find out the underlying cause and identify the site of leak, which you have addressed this between lines 47 and 49.

Reply 2: This point has already been addressed above as the first item listed under 'major issues'.

Comment 3: Line 105. During "severe" vomiting.

Reply 3: The word 'severe' has now been included in the relevant sentence (p.5).

Comment 4: Line 121. It may be more appropriate to state "movement of chyle into the thoracic space" instead of "upstream" to avoid confusion

Reply 4: Thank you for this suggestion – we have altered the text accordingly (p.5).

Comment 5: Line 137. Is it "in chylous ascites" or "in ascites"?

Reply 5: We apologize for any confusion here. We have adjusted this sentence (p.6) to clarify that it is raised intra-abdominal pressure in the presence of ascites (i.e. not specifically chylous ascites) that can contribute to thoracic duct obstruction.

Comment 6: Line 218 to 219, equivalent mg/dL should be provided.

Reply 6: We have now included the equivalent values (p.8).

Comment 7: Line 257, "most commonly used" may be a better alternative than " 'gold standard' ", especially the meaning of the quotation marks is unknown.

Reply 7: Thank you for this comment. We have adjusted this sentence to state that 'CT remains central to thoracic imaging...' (p.10), highlighting its important role in identifying underlying structural lung pathology.

Comment 8: Line 257, "contrast" CT or "plain" CT?

Reply 8: We thank the reviewer for this comment. The specific application of CT in chylothorax imaging may vary according to the clinical question being asked (e.g. 'where is the site of injury?', versus 'is there an underlying malignancy?'), and could

involve both contrast and non-contrast imaging. We have therefore avoided stipulating simply ‘contrast’ or ‘plain’ CT, but have adjusted the sentence to emphasize that both contrast and non-contrast CT may be utilized in this setting (p.10).

Comment 9: Line 285, “chyle” leak?

Reply 9: This statement has been adjusted from ‘chylus’ to ‘chyle’ accordingly (p.11).

Comment 10: Line 322, Guideline-directed medical therapy (GDMT) is a more proper term than simply “diuretics” for heart failure.

Reply 10: Thank you for this suggestion – we have adjusted the relevant sentence to include this terminology, whilst emphasizing that diuretic therapy is usually employed preferentially (p.12).

Comment 11: In line 330, are the authors talking about MCT supplements?

Reply 11: We apologize for any confusion here. The relevant sentence was simply referring to the mode of absorption of medium chain triglycerides (MCTs) in general, which occurs directly into the portal venous system (in contrast to long-chain triglycerides). We have adjusted this sentence slightly to indicate that this also applies to MCT supplements that patients may use (p.12).

Comment 12: Figure 2, left lower corner: consider writing TD embolization instead of TDE, to align the presentation with TD ligation in the same box.

Reply 12: Thank you for this suggestion. This figure (now named Figure 3) has now been adjusted in line with Reviewer F comments to make this less ambiguous and with greater clarity. We have adjusted the terminology contained within this figure accordingly, including use of the full terminology ‘thoracic duct embolization’ and ‘thoracic duct ligation’.

Comment 13: Consider adding a figure in the text showing the common (and clear appearance if available) milky appearance of chylothorax.

Reply 13: We thank the reviewer for this comment. Whilst the inclusion of such a figure would be ideal, we unfortunately do not have a picture available to us to demonstrate this appearance. Since it would require a potentially lengthy process of obtaining permission to use an image from an alternative source, we feel that the description we have provided is sufficient for the purpose of this review article.

Reviewer D

Comment 1: Methods are not well described for how a comprehensive review was conducted.

- We apologize for not including this detail in our original submission. We have now included a brief statement regarding our approach to conducting this review (see Introduction, p.3).

Comment 2: Authors should consider to use more recent literatures in pharmacological and surgical techniques.

- Thank you for this comment. We have not come across any additional information on newer pharmacological or surgical techniques beyond the various methods mentioned. However, we have aimed to include some more recent references for these approaches in the relevant sections where possible, and have updated the reference list accordingly.

Comment 3: Paragraphs 362 and 372, would be improved by describing outcome results related to medications and variation dosage.

- Thank you for this suggestion. We have now included information on outcomes in the relevant sections (p.13).

Comment 4: Line 405 prolonged chest tube drainage is misleading by implying immunosuppression is linked to chest tube rather than depletion of white blood cells loss as a result of chylothorax.

- We apologize for any confusion this sentence might have caused. We have edited and re-worded this for clarity (p.14).

Comment 5: In interventional radiology section more in depth dissection about different IR methods e.g.

<https://doi.org/10.1016/j.xjtc.2022.12.006>

<https://doi.org/10.1016/j.jvir.2022.05.007>

- Thank you for this suggestion. We have now included a short paragraph on these additional methods (p.16).

Reviewer E

Comment 1: In general, it is a good review about chylothorax but the authors must add/change two points. First, pleural fluid cytology is important. The white blood cell differential of fluid from chylothoraces typically has a predominance of lymphocytes, usually greater than 70 percent of the total nucleated cell count, reflecting the cellular composition of chyle [1]. Normally, the chylothorax is composed by lymphocytes matures but in non-traumatic chylothorax by hematology diseases lymphocytes with atypic morphology can be reported. However, in pseudochylothorax, although it has been described that there is a predominance of lymphocytes in 61% of cases... there may be a predominance of polymorphonuclear cells, as occurs in 39% of cases, which in chylothorax would be very rare. [2]. Furthermore, the presence of cholesterol crystals, although rare, is diagnostic of pseudochylothorax.

Reply 1: We thank the reviewer for this comment. We have incorporated the above information relating to the inclusion of pleural fluid cytology and relevant cell differential of chylothorax and pseudochylothorax as a new paragraph at the end of the

'pleural fluid analysis' section (p.9). We have also updated information relating to the identification of cholesterol crystals as a supporting diagnostic criteria of pseudochylothorax, both in the text (p.8) and within Table 2.

Comment 2: Second, imaging tests, in an initial clinical investigation, only can confirm the presence of pleural effusion, but their role is very limited for the diagnosis of chylothorax. In the abstract, the authors say: "Diagnosis relies on pleural fluid analysis and imaging". Although, in the article is explained correctly, in the abstract is not correct and the authors must change it for a correct sentence like "Diagnosis depends on appropriate pleural fluid analysis, supported by various imaging studies."

Reply 2: We thank the reviewer for this comment. As above (see Reviewer C comments, first point), we have now adjusted the relevant sentence in the abstract to remove the word 'imaging' when referring to diagnosis of chylothorax; the subsequent sentence clarifies that various imaging techniques may be utilised to support the diagnosis (p.2), which is also emphasized in the conclusion (p.17) and new clinical practice points box.

Reviewer F

This is a good review of chylothorax as there is no guideline for the management of chylothorax. Following is the recommendation.

Comment 1: It is better to have images of anatomy.

Reply 1: We thank the reviewer for this suggestion, and agree that the inclusion of an image would aid the description within the manuscript. We have now included a diagrammatic representation of the relevant anatomy within this section (now Figure 1).

Comment 2: In Pathophysiology section, you should mention that iatrogenic injury during surgery includes not only esophageal surgery but also lung resection for cancer, CABG, thoracic aneurysm repair, heart transplant, trauma and lung transplant.

Reply 2: Thank you for this comment. We have included an additional sentence in the relevant section (p.4) to highlight that these other surgeries are also a risk for iatrogenic chylothorax.

Comment 3: You mentioned milky fluid in pleural space occur only 22-44% of patients, but in the real clinical settings, we never suspect chyle leak if pleural fluid is not milky even after esophageal surgery. In which situation, we should perform pleural fluid analysis if the fluid is not milky.

Reply 3: We thank the reviewer for this comment. We have adjusted the relevant introductory sentences to the 'Diagnosis' section of the manuscript (p.7) to emphasize that pleural fluid analysis (as well as maintaining a high index of suspicion) is central to the process of diagnosing chylothorax, and that this should be performed even in the absence of classical macroscopic features (i.e. milky appearance of pleural fluid). The following sub-section on pleural fluid analysis extends this point by highlighting that chylothorax may present with a number of different appearances of fluid and, as such, it is not possible to diagnose chylothorax on the basis of appearances alone.

Comment 4: If patients fail conservative management (drainage, diet, medication), which do you recommend, surgery or interventional radiological approach? I believe we should consider interventional radiological approach first as this is less invasive and less complications. This is the most important part. Every doctors starts with conservative management, and everyone is discussing a lot what to do next if conservative management fails. You should comment about the sequence of management. Figure 2 is too ambiguous.

Reply 4: Thank you for this comment. The management of chylothorax is clearly challenging and, in the absence of definitive evidence supporting an optimal approach, a suggested flow-chart for management of this condition is necessarily based in large part on best available clinical judgement. Nonetheless, we agree that starting with more conservative approaches is sensible – we have modified the Figure (now named Figure 3) to highlight conservative management options more prominently at an early stage in

the suggested treatment algorithm, particularly in the case of non-traumatic chylothoraces. We have also made some adjustments to simplify the Figure and make this clearer for the reader, and to reduce ambiguity in the message conveyed. Whilst we agree that the use of interventional radiology methods may be preferable in some circumstances, this will depend heavily upon local availability and expertise, as well as whether individual patients are suitable for definitive surgical versus radiologically-guided treatment strategies. As such, we have emphasized in our modified Figure that it is essential for these decisions to be informed by multi-disciplinary team discussion, taking into account patient suitability and extent of ongoing chyle leak (i.e. high versus low volume). We feel this updated Figure provides a more concise representation of our suggested treatment algorithm, whilst incorporating the query raised by the reviewer above in a less ambiguous manner.

Comment 5: Please describe about needle disruption of the retroperitoneal lymph nodes. This is the newer interventional technique for chylothorax.

Reply 5: Thank you for this suggestion. We have now included mention of this technique within the relevant section (p.16).