Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-23-1457

Reviewer A

Comment 1: The authors report their experience inserting very small bore (less than or equal to 10 French) chest drains for pleural effusions, describing a cohort of 484 drains placed in 330 patients over a 3 year period. The most common drain sizes were 6 and 8 F, and the most common indications were malignant effusion and organ failure. Overall 40.9% of drains had at least one complication, the most common of which was need for an additional drain in 20.5%. Complications were more common in empyema and malignant effusion. The rate of treatment failure of very small bore drains was also higher for malignant effusion (25.5%) and empyema (56%) than in organ failure (9.5%) or simple parapneumonic effusion (12.5%). Interestingly, specialists had a higher rate of complication than residents. The authors conclude that very small chest drains were effective in the vast number of cases of simple pleural effusion, although less so for empyema. They also suggest in the discussion that the short-term failure rate of 25.5% for very small chest drains in malignant effusions is comparable to the rate of success of chemical pleurodesis for malignant effusions.

Strengths:

-Large cohort of patients and chest drains with a variety of diagnoses

-Well-described results in terms of drains used, technique, and complications

- Rational discussion of strengths and weaknesses including potential limitations in empyema in the absence of a hospital protocol for flushing of chest drains

Weaknesses:

-Unavoidable risk of bias inherent to retrospective cohorts—unknown details of patients who may have received larger chest drains outside the radiology department

-Unavoidable lack of clarity regarding time each diagnosis was made and whether this information influenced the type of drain used

Overall a nice description of a large cohort of patients who received very small

I'm also not sure that the comparison in the discussion of short-term failure rate in malignant effusion to the rate of successful outcome of malignant effusion with pleurodesis is valid. This is comparing surgery or need for a new drain to pleurodesis success, which is a more complex outcome that may be affected by many more variables (such as whether or not the lung is expandable). With all that said I think this is a well written report that could use minimal revision.

Reply 1: We thank the reviewer for this thorough and constructive evaluation of the paper and we agree about the strengths and weaknesses. Regarding the risk of bias from potential missing data on larger drains received in other departments – we did capture larger drains received through the electronic medical records (covering the Departments of Thoracic Surgery and Respiratory Medicine, where larger drains are inserted); and this data is used for evaluating the rate of requiring additional drains (after insertion of the first small bore drain). As the aim was to evaluate complications following small bore drains, data on larger bore drains as the first drain would have been beyond the scope of this article. We totally agree about the limitation relating to the timing and nature of clinical diagnosis in retrospective analyses as this, which is discussed in the paper.

We agree with the reviewer that the comparison with outcomes after pleurodesis in malignant PE is difficult (also as we lacked data on frequency and type of pleurodesis in our study, as discussed by other reviewers). This has been removed (see below).

Changes in the text: The comparison with pleurodesis in malignant PE was removed (page 12; row 235).

Reviewer B

Thank you for the request to review this retrospective cohort study on outcomes of small bore drains for the management of pleural collections. In general, it is well written and only involved straightforward descriptive statistics for which I don't have any objections:

Major comments

Comment 1: Surgery is not always a "failure" of drain management. Drains do not address the underlying cause of the collection, nor does it prevent recurrence or surgery. In fact, it is often used as a bridge [symptomatic relief] to surgery, and if so would be considered "successful" despite requiring surgery. Authors should consider redefining this outcome.

Reply 1: We agree with the reviewer and this outcome has been renamed to “repeat intervention” as suggested.

Changes in the text: “Treatment failure” changed to “repeat intervention” throughout the article.

Comment 2: It is too simplistic to state that a small bore drain has high failure rate for pleural infection. Rather, a small bore drain has a high failure rate in the presence of loculation and/or thick pus. In early para-pneumonic effusions / empyema without loculi, there is no reason why a small bore drain would not be sufficient?

Reply 2: We thank the reviewer for raising this important point. As per Comment 3 below, treatment failure has now been renamed “repeat intervention”. We agree that the rate of repeat intervention is lower in uncomplicated PEs without loculi. Details on pleural ultrasound were unfortunately not available in this retrospective study but we agree that provides important clinical information. Very small bore drains were effective in uncomplicated PE (as discussed by the Reviewer) whereas the complication rate was high in cases of established empyema. The importance of pleural ultrasound in this evaluation has been highlighted in the revised Discussion section, including that the presence of echogenic fluid and/or septation could be a reason to use larger-bore (than very small) chest drains (such as 12 Fr).

Changes in the text: Added to Discussion (page 15; row 304): “Pleural ultrasound can inform the need and type of drainage, with echogenic pleural fluid or septa indicating an increased risk of complications when using very small chest drains and the need for larger drains (such as 12 Fr or larger)”.

Comment 3: In think "repeat intervention" is more accurate rather than "treatment failure", as the two are not synonymous.

Reply 3: We agree with the reviewer and this is a great suggestion. The outcome has now been renamed as “repeat intervention” as suggested.

Changes in the text: Please see reply 1.

Comment 4: A multivariable [logistic] regression would be useful, rather than large number of tables to be able to discern the important components for repeat intervention.

Reply 4: Of the 2 tables in the article, Table 2 reports the multivariable logistic regression for all the outcomes.

Changes in the text: That the multivariable model is reported in Table 2 has been clarified in the Results section (page 10, row 204):

Reviewer C

This is a retrospective study looking at treatment failure and complications of ultrasound-guided very small bore chest drains (6-10 F) and a single center placed by the radiology section. These are the issues with the study:

Comment 1: Majority of the times the diagnosis/etiology of the pleural effusion was not known at the time of insertion of the chest tube. This is not a standard practice to place a chest tube in the pleural effusion without a known etiology. Chest tube is not standard treatment for or pleural

effusions. Indications for chest tube and pleural effusions are specific depending on etiology and patient's symptomatology. The effectiveness of the chest tube depends upon the etiology of the pleural effusion. The standard mode of practice and majority of instances is to first establish the etiology of her pleural effusion and then determine the treatment which could be simple observation, simple drainage with thoracentesis, chest tube if indicated, indwelling pleural catheter or surgical intervention.

Reply 1: We thank the reviewer and agree that diagnosis is a key first step that influences the management of PEs. As the aim of the present study was to evaluate outcomes after placement of a small bore chest tube, this was the point of inclusion in this study. Any prior diagnostic analyses to establish the diagnosis (such as thoracentesis) were not included. However, the likely diagnosis at the time of small chest tube insertion was evaluated from the medical records (which would be influenced by the prior examinations). Also, patients who did not receive a chest tube but was solely observed were not included in this study, as per the study aim.

Changes in the text: None.

Comment 2: The patient with a known malignant pleural effusion it is not a common practice to place a small bore chest tube. He has symptomatic patient with known malignant pleural effusion the most common option is to place an indwelling pleural catheter with daily or intermittent drainage.

Reply 2: We agree with the reviewer that this is now an approach recommended by many (or most) clinical guidelines, but the management of patients will be influenced by multiple factors. Patients may present to and be admitted from the ED with a large PE, which will then often receive a chest tube (small bore) through the radiology department at our hospital due to the availability (also nighttime) and as it enables samples to be collected for analyses (many being available to the rounds the next morning). Also, as the aim was to study outcomes after small bore chest drain, this was an inclusion criterion in the present study. Patients receiving an indwelling pleural catheter were thus not included, as per the study aim.

Changes in the text: None.

Comment 3: In patient with known empyema a chest tube was inserted and fibrinolytics along with dornase are instilled into the pleural space to help drainage. Majority of the time surgery is

not indicated. There is no mention of instillation of fibrinolytics and dornase in the study for empyema.

Reply 3: We thank the Reviewer for raising his question. This study pertained only to very small chest drains, and while fibrinolytics were used at the Departments for empyema during the study period (but specific data on this was not captured as it was not considered a complication), this treatment is not given through very small chest drains, and would be a clinical indication for repeat intervention with a larger-bore drain, which was captured as a repeat intervention after the very small drain.

Changes in the text: Added to Limitation (page 14; row 292): "Data on pneumothorax, pleural fibrinolysis, or pleurodesis were not evaluated"

Reviewer D

Comment 1: Few minor errors like line 163- 'sore' size. Need for new drain 20.5 %.

Reply 1: Thank you, corrected.

Changes in the text: Corrected in these lines.

Comment 2: Interesting definition of complication- need for a new drain perhaps not a complication unless the small drain is blocked- can the authors elaborate why 20.5% people needed new drains? Or make it clearer – I note line 172- blocked with what?

Reply 2: We thank the Reviewer for these good points. New drain has now been included in a renamed outcome "repeat intervention" to clarify this. The categorization of drain blockage has now been more explicitly defined.

Changes in the text: Added to Methods (page 7; row 160): "Drain blockage was defined as documented stopped drainage through the very small chest drain despite remaining PE without signs of drain misplacement."

Comment 3: Findings- line 186-191- this is not correct. Association is not correlation. I would argue and change that your success rate is 74.5% rather than lead with your failure rate- but surely this figure is dependent on your sclerosing agent- so it is not a measure of your drain but of your agent used. So that is not the correct conclusion to get to- it would be better to say we managed to drain all fluid in 75% of patients etc. there is some evidence about larger drain sizes being better at pleurodesis: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5346594/ - you have found the reverse - you really need to look at what screlosing agents were used

Reply 3: Findings including associations are reported in relation to the rates of the outcomes (complications) throughout the article for consistency. Data were not available on the sclerosing agents administered, which has been added to Limitations.

Changes in the text: Added (page 14; row 292): "Data on pneumothorax, pleural fibrinolysis, or pleurodesis were not evaluated."

Comment 4: I don't understand why you use these very small drains- is it because of lack of availability of 12Fg drains which are more standard? Or cost? Why do radiology insert them rather than respiratory physicians? I note line 213-216- this needs to come way earlier in the article.

Reply 4: We thank the Reviewer for raising this important point that needed to be clarified in the manuscript. In clinical routine care at our Hospital, very small-bore chest drains are commonly inserted through the Radiology Department mainly due to the feasibility and high availability (compared to respiratory physicians), often at the time of admission from the emergency department.

Changes in the text: Added to Introduction (page 5; row 93): "Insertion of very small chest drains using one step technique is often used at our Radiology Department as it is easy to learn, faster (compared to insertion using Seldinger technique), and considered safe as the use of ultrasound guidance allow imaging of the trocar tip during insertion. "

Comment 5: Line 193- 19% is not close to 23%. Line 193-200 means that you should not be using the small bore drains for empyema. You might have better success with slightly larger drains like 12F. There is no evidence that larger than those are required initially (look at the Pleural disease guideline by the British Thoracic Society, published mid 2023). Can you also

compare to the empyemas that did not have 'drain failure'? their ph was lower/higher? More septations? Were they sicker to start with?

Reply 5: We agree with the Reviewer's interpretation, which is in line with the interpretations regarding empyema in the article. Data on pleural pH and septations were unfortunately not available.

Changes in the text: The Clinical Implications section (page 15; row 304) has been expanded to include: "Pleural ultrasound can inform the need and type of drainage, with echogenic pleural fluid or septa indicating an increased risk of complications when using very small chest drains and the need for larger drains (such as 12 Fr or larger).". The BTS 2023 clinical guidelines has been added as reference in the article.

Comment 6: Line 202- one way to interpret this is that you need to suture the drains. It is common practice to suture drains. Line 213 – shows some of your reasons, but these need to come way before in your article

Reply 6: The very small chest drains used in the study were applied in accordance with the instructions of the manufacturer (as stated in the Methods section). We agree that the finding of a relatively high rate of dislodgement is clinically relevant and this has been added to the Clinical Implications section (please see below).

Changes in the text: Added to Clinical Implications (page 15; row 310): "[…] the relatively high rate of drain dislodgement suggest the need to fixate and secure the very small drains more effectively such as through drain suture.". The reasons for inserting the very small drains have been added to the revised Introduction as per Reply 4.

Comment 7: I would suggest a major re-write of the article with the above changes highlighted. You essentially have a descriptive study, and you should stick to the observational nature of that- you can perceive trends but not form conclusions

Reply 7: The article has been revised in accordance with the Reviewer suggestions. The conclusion has been revised to better reflect the observational nature (relations/associations).

Changes in the text: Conclusion revised (page 15; row 316) to: "A single small-bore chest drain (6-10F) was associated with low rates of complications in simple PEs, but showed high rates of complications in empyema, with the frequent need of additional drains or surgery. These findings support use of larger drains and early consultation with a thoracic surgeon in empyema."

Reviewer E

Comment 1: Authors suggested that small chest tube was able to drain parapneumonic effusion effectively. They need to clarify whether this is a simple pleural infection or complicated pleural infection which is usually very difficult to drain without adding antifibrinolytic therapy, pleuroscopy or VATS.

Reply 1: We agree and have added a clarification in the revised article.

Changes in the text: Addition in Methods under Data collection (page 7; row 159) "Parapneumonic effusion was defined as simple PE without any finding of empyema on the same side as a diagnosed pulmonary infection."

Comment 2: The confounding issue in any small bore chest tube is the need for routine flushing of the tube and thus it is difficult to draw conclusion that large bore chest tube is needed but rather probably advocating for routine flushing and escalating to larger bore tube if needed. This should be reflected in the discussion section.

Reply 2: We agree with the Reviewer and this has been added to the revised Discussion.

Changes in the text: Revised Discussion (page 13; 257): "One reason for our high rate of blockage in empyema could be that at the time of this study there was no hospital-wide routine for flushing small chest drains, and it was up to the separate wards to decide if and how this was done. The need for routine flushing of small chest drains is a potential confounder when comparing outcomes of small versus larger drains."

Reviewer F

I read with interest the manuscript entitled "Complications and treatment failure of real time ultrasound guided small-bore chest drains for pleural effusions of different etiology". The authors analyse the outcome of very small bore chest drains (6-10 Fr) and their efficacy in relation to the pleural effusion etiology.

The topic is interesting considering that literature on this the use of such small tubes is still limited. English language is fluid and acceptable. The aim of the study is clear and the background is well explained. Methods are well described. However, results could be improved for a better comprehension of the outcomes and authors conclusions. For example, considering a treatment failure only surgery or a need for a new drain within 2 weeks from the removal is reductive. Often the need for a new drainage after removal is due to the status of the underlying pathology (e.g. cardiac failure or pleural malignancy) and does not depend on the caliber of the drain. Probably, a residual PE before removal or the necessity for a new drain during hospitalization could have better described a treatment failure.

Moreover, the authors conclude that "A single small-bore chest drain (6-10F) was successful in the vast majority of simple PEs and in most malignant PEs" suggesting that a very small chest tube could be sufficient also in malignant PEs. This is conflicting with the results of the study where a single 6-10 Fr catheter present about 50% of overall complications, 21% of blockage and 25% of the need for a new drainage in case of malignant effusion.

I have some comments and suggestions:

Comment 1: Title: Clarify in the title that the study is focused on VERY small bore chest drains (6-10 Fr). This is in my opinion one of the strength point of this study and should be highlined in the title. In fact, guidelines regarding the management of small chest drain are available but are generally limited to 12-16 Fr tubes.

Reply 1: We agree with the reviewer, and the title has been changed as suggested. Moreover, the conclusion was amended to reflect the relatively high rate of complications in malignant PEs.

Changes in the text: The title was changed to "Complications of ultrasound guided very small-bore chest drains for pleural effusions of different etiology". The conclusion of the abstract was changed to: "A single small-bore chest drain (6-10F) was successful in the vast majority of simple PEs, but had high complication rates in empyema with frequent need of additional drains or surgery. These findings support use of larger drains and early consultation with a thoracic surgeon in empyema."

Comment 2: Key Findings And Conclusions: The sentence "A single small-bore chest drain (6-10F) was successful in the vast majority of simple PEs and in most malignant Pes" in my opinion is speculative and a more cautious a more cautious conclusion (i.e. does not show similar efficacy for PEs) might be more appropriate. I agree with the authors conclusions regarding simple PEs and empyema.

Reply 2: We thank the Reviewer – this is a good point. We agree and the Key Findings have been changed in accordance.

Changes in the text: Key Findings (page 2; row 28): "This consecutive cohort of 484 very small chest drains (6-10 French [F]) in 330 people found that the intervention was related to a low risk of complications in simple pulmonary effusions (PEs), but high rates of complications and repeat interventions in empyema." Conclusion (page 15; row 341): "A single small-bore chest drain (6-10F) was successful in the vast majority of simple PEs, but showed high rates of complications in empyema, with the frequent need of additional drains or surgery. These findings support use of larger drains and early consultation with a thoracic surgeon in empyema."

Comment 3: In my opinion the choice for a large or small catheter depends on the ultrasonic characteristics of the effusions. In most cases, the presence of septa or echogenic fluid with thickened pleura is suspected for empyema and we proceed with a large tube. Do you think this could be enough for choosing the size of the tube?

Reply 3: We totally agree with the reviewer on the importance of pleural ultrasound in this regard.

Changes in the text: (page 15; row 329): "Pleural ultrasound can inform the need and type of drainage, with echogenic pleural fluid or septa indicating an increased risk of complications when using very small chest drains and the need for larger drains (such as 12 Fr or larger)."

Comment 4: Discussion: From what we understand, your study is based on the insertion of chest drain and not on a pleurodesis procedure. Therefore, comparing your outcomes with those in the literature regarding the success rate of pleurodesis in malignant PEs is not correct in my opinion and should be removed.

Reply 4: Thank you for raising this important point, which was also raised by Reviewer A (Comment and Reply 1). This has been removed.

Changes in the text: (page 12; row 260): the comparison with pleurodesis in malignant PE was removed, as suggested.

Comment 5: Another limitation of the study is surely the absence of a control group treated with larger tubes that cannot allowed statistical analysis. This should be highlighted in "limitation" section.

Reply 5: We agree and this is now acknowledged as a limitation.

Changes in the text: (page 14; row 314): "The observational design and lack of a comparable group treated with larger-bore drains prevents a direct comparison of outcomes."

Comment 6: Table 2 seems to confirm that a very small drain in malignant PE has a statistically significant more complications, blockage rate and treatment failure (bold character). Please report p-value and discuss this aspect in the discussion section.

Reply 6: We agree and thank the Reviewer for highlighting this finding. In accordance with major statistical reporting guidelines, p-values are not reported (as those are often misinterpreted by readers). Instead (as recommended) we report point estimates with 95% confidence intervals.

Changes in the text: The legend to Table 2 has now been clarified (page 22) to: "Associations with risk of complications analyzed using multivariable logistic regression, expressed as adjusted odds ratios (aOR). Each aOR is adjusted for all the other factors in the table. Estimates that were statistically significant (defined as a 95% confidence interval not including the value 1) are marked in **bold**."

The first paragraph of the Discussion has been revised (page 12; row 256) to:

“In this large, consecutive cohort study of 484 very small chest drains (<10F), almost half of the drains were inserted to treat malignant pleural effusions with a short-term failure rate of 25.5%. Compared to PEs due to organ failure, the odds of any complication was increased in malignant PE by 2.5 times (95% CI, 1.5-4.4) and in empyema by 7.3 times (95% CI, 2.9-18.6).”

Reviewer G

Comment 1: Although retrospective in nature, this is a well-conceived and very well-written manuscript examining the complications of small-bore chest tubes. This paper adds to the growing body of evidence that "smaller is not always better", especially for empyema and malignant pleural effusion. There is a role for small-bore chest tubes, but clinicians need to better understand those indications. This paper will further help educate them.

Reply 1: Thank you.