

Peer Review File

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Reviewer A

Comment 1: In the context of patients suspected with esophageal perforations, management decisions should be guided primarily by the degree of contamination rather than the aetiology of the defect. The decision to proceed with operative or non-operative management is influenced by the extent of mediastinal and pleural contamination and the degree of systemic sepsis, not merely the aetiology. In this context, it is unclear why the emphasis on performing esophagram at the presenting site (irrespective of the recommendation of the American College of Radiology).

Authors' Response: Thank you for your comment. We agree that operative management should be guided by the clinical status of the patient. It is our intention that this manuscript focuses primarily on the decision to transfer at patient in the setting of suspected esophageal perforation, not on the operative management. In patients who are highly likely to have an esophageal perforation either based on diagnostic studies or history and physical evaluation, transfer to institution capable of definitive management should not be delayed.

Changes in Text: The title of this manuscript is intentionally, "Esophagram Should Be Performed to Diagnose Esophageal Perforation Before Inter-Hospital Transfer." We have clarified this message. **We have added additional emphasis on the importance of not delaying transfer on lines 270-274.**

Comment 2: With the widespread availability of CT scanners in the United States (as exemplified by routine use of CT in diagnosing acute appendicitis), it would seem incongruent that CT esophagography has not supplanted esophagram (CT esophagography for evaluation of esophageal perforation: *RadioGraphics* 2021; 41:447–461). "CT esophagography has been shown to be at least equal to fluoroscopic esophagography for diagnosis of esophageal perforations with the key advantage of 24-hour and 7 days a week availability in most hospitals; finally, this technique provides further benefits because it helps diagnose extraesophageal conditions."

Authors' Response: We understand that there are some radiology based recommendations to supplant esophagram with CT imaging. We have discussed this on Lines 324-329. We would like to emphasize the increased specificity that esophagram adds (98.9% vs 79.8%, manuscript reference 17) which is especially important in determining the need for transfer in a clinically stable patient. Additionally, we believe the benefit to esophagram (over CT) is the dynamic nature of the study which allows for more information regarding the location and extent of perforation to guide endoscopic and surgical intervention.

Changes in Text: **We have added additional acknowledgement of the ability of CT to diagnosis extraesophageal conditions, lines 329-330.**

Comment 3: It will be helpful for the authors to investigate and comment on the availability of esophagogram versus CT imaging at the referring institutions, to ascertain whether their recommendation that the referring institution obtain an esophagram is feasible.

Authors' Response: We agree that this is an important factor to identify, especially in light of our recommendations to obtain an esophagram prior to transfer. This information is not available in the transfer records we reviewed for this analysis.

Changes in Text: No changes were made due to limitation of data.

Comment 4: Data analysis: “Multivariable logistic regression was performed to identify factors associated with diagnosis. Covariate selection followed a two-step procedure”. Step-wise regression (forward or backward elimination) approach: although stepwise regression is popular, many statisticians agree that it should not be used as it's riddled with problems. To mention only a few: the problem of multiple hypothesis testing, rate of Type-I and Type-II error increases significantly; issue of collinearity, bias in parameter estimation etc. It would be wise to refrain from step-wise approach and select potential predictors based on clinical relevance. (Step away from step-wise: Smith J Big Data (2018) 5:32 <https://doi.org/10.1186/s40537-018-0143-6>).

Authors' Response: We appreciate and understand that literature exists regarding the implications of step-wise regression. As mentioned, this is currently still a standard and accepted practice in surgical literature. We have reviewed the coefficients of the predictors that are considered to be clinically significant and these are included in the model.

Changes in Text: We have added to the limitations section of the manuscript a statement on the limitations of step-wise logistic regression, lines 349 to 353.

Reviewer B

Comment 1: 63.1% of patients were confirmed to have esophageal perforation in the tertiary center. What is the method used as the standard to confirm or rule out esophageal perforation at the tertiary center? From table 2, it appears that different protocols were used for patients at the tertiary center as well (Esophagram not obtained in 44.6% of patients, CT not obtained in 86.2% of patients).

Authors' Response: Esophagram is the standard to confirm/rule out esophageal perforation at our tertiary center. In the 29 (44.6%) of patients who did not receive esophagram at the tertiary center, many had an esophagram with obvious findings at the OSH (n=10, 34%) or were sick enough to go direct to OR (n=11, 38%) for operative intervention. The remainder were due to attending thoracic surgeon clinical decision (eg: history and physical consistent with perforation and enteric contents draining from chest tube placed at transferring hospital, obviating need for additional studies prior to surgical intervention).

Changes in Text: Phrasing to indicate esophagram is the standard of care at our institution has been added to line 292.

Comment 2: It may be more informative to provide the sensitivity/ specificity/ AUROC for esophagram/ CT/ blood tests/ clinical predictors that were done in the outside hospitals.

Authors' Response: We agree that this specific institutional data would be beneficial, however we are unable to obtain this granular, and institution specific, data. In place of this, we have cited the available literature on sensitivity and specificity of esophagram/CT throughout the manuscript.

Changes in Text: We have added acknowledgment of clinical predictive factors, including symptomatology and clinical signs to lines 270-274. We have added to the limitations the lack of information from the transferring hospital, lines 348-349.

Comment 3: 27.7% had unknown transferal time. Is it possible that some patients had an initial correct diagnosis of small concealed perforations in outside hospitals? But a long delay in transferal may have allowed time for healing and led to a diagnosis of no perforation in the tertiary center.

Authors' Response: While this is a possible explanation for no perforation identified at the tertiary center, transfer time was typically within a day of initiation of transfer. However, we have previously acknowledged this in the limitations, lines 342-345. In the 47 patients with known transfer time the majority have a transfer time of less than 4 hours, with only 1.5% having a transfer time greater than 12 hours. Based on this, it is conceivable that 27.7% with missing data would have a similar distribution of transfer time with the majority being under 4 hours.

Comment 4: It would be more preferable to include more blood tests parameters in the analysis, such as hemoglobin level.

Authors' Response: Thank you, we agree that additional blood test parameters would be beneficial; especially with the understanding that in a clinically unstable patients or those at risk for decompensation transfer should not be delayed. We did review WBC and lactate levels, however did not evaluate hemoglobin levels due to the expectation that these would not be as deranged as WBC/lactate given patients with esophageal perforation do not develop hemothorax or anemia. As such, unfortunately, this data is not readily available at this time for analysis but agree this is worthy of further investigation and perhaps creation of a formal algorithm.

Comment 5: Page 6 line 193, the etiologies should be for suspected esophageal perforation rather than for esophageal perforation? And what are the other etiologies for suspected esophageal perforation other than spontaneous and iatrogenic

Authors' Response: Thank you for pointing this out. We have adjusted the manuscript accordingly.

Changes in Text: Line 193 has been modified to reflect wording “suspected esophageal perforation”.

Comment 6: Since 96.9% of all patients already had CT at outside hospitals, it may be easier to add on CT esophagram on top of the routine CT for diagnosing esophageal perforation before transfer? The discussion part did mention about the relative sensitivity/ specificity of CT esophagram vs esophagram, but if CT esophagram can perform with 100% sensitivity + 79.8% specificity, this would already be a good diagnostic performance, and may already be suitable as a first-line test in outside hospitals

Authors' Response: This was similarly raised by reviewer 1. We agree that CT esophagography is a reasonable recommendation when esophagram cannot be performed. However, we believe the benefit to esophagram over CT is the dynamic nature of the study which allows for more information regarding the location and extent of perforation to guide endoscopic and surgical intervention. As noted, CT esophagram is an acceptable alternative when esophagography cannot be performed.

Changes in Text: Lines 330-3332, have be altered to acknowledge the high rate of CT scan performed at OSH and the suggestion that it may be conceivable to add on a dedicated CT esophagram to the routine protocol.

Comment 7: What were the final diagnoses of the 24 patients who were eventually shown to not have esophageal perforation?

Authors' Response: Of the 24 patients who were determined not to have esophageal perforation the following final diagnoses were identified: Esophageal Injury/Laceration, Not Full-Thickness (n=7, 29%); Esophageal Stricture (n=2, 8%), Esophagitis (n=1, 4%); Hiatal Hernia (n=3, 13%); Gastro-Broncho-Pleural Fistula, Related to Prior Nissen (n=1, 4%); Pharyngeal Abscess (n=1, 4%); Pneumomediastinum without esophageal perforation, Not Otherwise Categorized (n=8, 33%); Hemothorax (n=1, 4%).

Changes in Text: The above distributions have been added to lines 215-219.