Journal of Clinical and Translational Research
Peer review process file 07.202106.014

Omental patch repair of large perforated peptic ulcers ≥25mm is associated with higher leak rate

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Handling editor:
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Review timeline:

Received: 9 September, 2021
Editorial decision: 26 October, 2021
Revision received: 2 November, 2021
Editorial decision: 7 November, 2021
Published online: 29 November, 2021

1st Editorial decision
26-Oct-2021

Ref.: Ms. No. JCTRes-D-21-00160
Omental patch repair of perforated peptic ulcers ≥25mm is associated with three-fold higher leak rate for every 10mm increase in ulcer size
Journal of Clinical and Translational Research

Dear Dr Chan,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Nov 25, 2021.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: Dear Authors
A large series on perforated peptic ulcers with acceptable clinical outcomes. I have few critics fkr the manuscript.
1. Title should omit 3 fold etc. Just keep as 25mm Nd larger ulcer.
2. Conclusion and discussion i am unclear. Is large ulcer 25 mm and larger associted with higher leak or higher mortality or both? Csn pls clarify this in abstract, conclusion and make it clear to readers.
3. What sutures did you use to repair? Silk or PDS? Or others?
4. Do you leave behind abdominal drains? For how long?
5. Do you insert NG tube? Whats your policy on NG removal.
6. Why in your series has only about 60% patients have free air on chest x ray? This is interesting. In my experience this is more than 80%. Any reasons?
7. You have less cancers in ulcer cases. Any explanation.?
8. Do you test peritoneal fluid and what about fungus and do you give antifungals?
9. Does your unit have endoscopic clipping available? Any experience to generate discussion on this.
Overall i feel the data is well presented and you have included limitations like not reporting on pneumonia and urinary or wound infections - so i accept it. If available, such data would be good to have.

Reviewer #2: The authors of this manuscript present an extensive retrospective case series profiling repair of peptic ulcer over a >12 year period while evaluating the relationship between size of the ulcer and leak rate. The center of study is clearly a high volume center, as the case volume is nearly 5 ulcers per month. While the data presented here do contribute some additional knowledge to the topic of perforated ulcer, the results are lacking some important information and the paper does not conclusively address the conclusions as stated in the final paragraph. The manuscript could be improved with addressing several major issues. Some specific comments include:
- There are additional characteristics of the patients and ulcers that are relevant but not included. Specifically, ulcer location (gastric/duodenal) is not described even though this is known to be relevant to leak rate.
- Can the authors please clarify that omental patch repair was the only method of repair included in this series? For instance, were any of these ulcers closed with primary repair first, then covered with an omental patch on top to buttress the repair? Or was this entirely ulcers that were not primarily repaired and only treated with omental patch?
- The rate of laparoscopic repair is noted only in passing in the manuscript, and is not able to be analyzed as an independent risk factor for leak, but the discussion contains a significant amount of direction discussing laparoscopic repair. This seems only peripherally relevant to the main point of the paper. Would edit this for discussion most relevant to the data being presented.
- The study would be greatly enhanced by stratifying additional outcomes by ulcer size as

well (malignancy, mortality, etc). In the discussion, the authors seem to (though not explicitly) use their results to compare to studies focusing solely on large or giant ulcers and make the conclusion that gastric resection may have worse outcomes. However, their data taken as a whole includes a majority of smaller ulcers. To more definitively establish a size cutoff for alternative methods of repair, need to consider outcomes in addition to leak rate.
- This is a significant amount of ulcers repaired by simple patch repair. How many additional patients were identified and excluded from analysis due to other types of repairs, such as gastric resection, pyloric diversion, etc?
- In the discussion, do not need the specifics of a power analysis of a proposed study. This is distracting. Can report a possible future study and patients needed, but other details should be removed.
- There are several references in the paper to an operating surgeon calling another surgeon with more experience for help. However, there is no data presented to support this suggestion, and I am unfamiliar with any other studies in the literature that support that older or more experienced surgeons have decreased rate of leak or other outcomes.
- On the description of baseline characteristics, perforation seen on CT scan is listed as 322 patients but 98.8%, which does not compute with an n=690. Please clarify.
- The leak is determined by drainage character or confirmed at operation in this study. Were drains used on every patient, or were there some patients that did not have surgical drains placed during the original operation? Is there any difference in leak rate between patients with or without surgical drains? Was any postoperative imaging used to monitor for leaks?
- The use of PPV and NPV would typically be used to refer to a test result, and this would seem to be more clearly referred to as a rate of leak by ulcer size. Consider revising table 4 to be more clear in the message the authors are trying to convey with this information.

Finally, I would mention that multiple times in the manuscript, the authors note that ulcer size has been related to leak rate in other studies and say that their findings are not novel or unexpected. If this is the case, why would the study be worth publishing? Would remove statements that diminish the work included here. It is important to acknowledge other studies that report findings similar to those presented, but it is important to demonstrate why the work here is important and how it may affect further studies or clinical outcomes. Would adjust the study to more comprehensively evaluate an appropriate cutoff for ulcer size to not only include leak rate, but rate of malignancy, mortality, and other complications to more definitively demonstrate a cutoff at which alternative methods of surgical management should be considered.

Reviewer #3: It's an excellent article. But the article did not mention how long it takes when the patient presented at hospital and was sent to receive the operation. It will be perfect if this is discussed in the article.

Authors' response

Date: 2 November 2021

Re: Manuscript ID JCTRes-D-21-00160: Omental patch repair of perforated peptic ulcers ≥25mm is associated with three-fold higher leak rate for every 10mm increase in ulcer size

Dear Editor-in-Chief and Reviewers,

We are thankful to you and the reviewers for the insightful critic and comments. We have enhanced the manuscript accordingly and enclosed below is the **point-to-point response** with the changes made in manuscript **(underlined in manuscript).**

In addition, we found some grammar and syntax errors, which we have rectified too. These edits are included in the last section of our response.

Yours sincerely,

Kai Siang Chan

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Reviewer 1

Dear Authors,

A large series on perforated peptic ulcers with acceptable clinical outcomes. I have few critics for the manuscript.

Comment 1. Title should omit 3 fold etc. Just keep as 25mm and larger ulcer.

Reply: Thank you for the suggestion. We have amended our study title to be: Omental patch repair of large perforated peptic ulcers ≥25mm is associated with higher leak rate

Comment 2. Conclusion and discussion i am unclear. Is large ulcer 25 mm and larger associated with higher leak or higher mortality or both? Can pls clarify this in abstract, conclusion and make it clear to readers.

Reply: We apologise for the confusion. We meant that increase is ulcer size is associated with higher leak rate. We have modified our conclusion to the following: However, our study demonstrated that increase in ulcer size is an independent predictor of OPL, with a 3.3 times increase in leak rate for every 10mm increase in ulcer size. Ulcer size of ≥25mm can be used as a guide in surgical practice to predict leak rate. It is however, not a good predictor of 30-day mortality.

In addition, we have edited the conclusion section in the abstract. It now reads as: Ulcer size increase in 10mm increases leak rate by 3.3 times. Ulcer size ≥25mm predicts OPL.

Comment 3. What sutures did you use to repair? Silk or PDS? Or others?

Reply: All omental patch repair was performed with PDS 2/0. We have included this in our methodology: Polydioxanone (PDS) 2/0 suture was routinely used for omental patch repair.

Comment 4. Do you leave behind abdominal drains? For how long?

Reply: All patients who undergo omental patch repair of perforated peptic ulcer have routine drain placement in view of risk of leak. Drains were kept in-situ until there was low drain output (typically defined as below 50ml peritoneal effluent) for two consecutive days, or were removed at surgeon's discretion.

We have included this in our methodology: A closed suction Jackson-Pratt® drain was routinely placed intra-operatively with intent to monitor for early detection of post-operative leak and prevention of intra-abdominal collection. Drains were removed when the effluent was below 50ml per day on two consecutive days, or at surgeon's discretion.

Common 5. Do you insert NG tube? Whats your policy on NG removal.

Reply: NGT is routinely inserted pre-operatively or intra-operatively for patients with perforated peptic ulcer. Timing of NGT removal is dependent on clinical improvement of patient, such as flatus passage or bowel opening. We have included this in the methodology:

Nasogastric tube (NGT) was routinely placed pre-operatively or intra-operatively for gastric decompression. NGT was removed according to clinical judgment which was determined by history, physical examination, and chart reviews. History of passage of flatus and bowel opening, soft and non-distended abdomen with active bowel peristaltic sounds, and less than 500ml output over past 24-hour period would prompt for NGT removal consideration. In alignment with enhanced recovery after surgery principles, every morning rounds a conscious deliberation was done if NGT withdrawal is safe.

Comment 6. Why in your series has only about 60% patients have free air on chest x ray? This is interesting. In my experience this is more than 80%. Any reasons?

Reply: We thank you for sharing your experience in this. We believe that the presence of free air on erect Chest X-ray is highly variable. Ultrasonography or CT imaging has higher sensitivities compared to Chest X-ray. This is supported by the consensus statements by the World Society of Emergency Surgery in 2020, stating variable incidence of free air in Chest X-ray ranging 30-85%.[1] A possible reason behind this is that patients present relatively early and majority have small ulcers. Volume of pneumoperitoneum may be too small to be detected on chest X-ray. In the context of patients with high index of suspicion for perforated ulcer and absence of free air on chest X-ray, we usually proceed with computed tomography of the abdomen and pelvis. We have not made any edits to our manuscript, hope this is acceptable.

1. Tarasconi, A., Coccolini, F., Biffl, W.L. et al. Perforated and bleeding peptic ulcer: WSES guidelines. World J Emerg Surg 15, 3 (2020). https://doi.org/10.1186/s13017-019-0283-9

Comment 7. You have less cancers in ulcer cases. Any explanation?

Reply: We have modified our discussion to address this issue as follows:

Our study reported low incidence of malignancy of 2.3% compared to existing literature. Hodnett et al reported 7.6% incidence of malignancy in 202 patients with perforated gastric ulcer,[28] while a review by Roviello et al. reported 10-16% incidence of gastric cancer in patients with gastric perforation.[29] Perforation of gastric cancer occurs more frequently at advanced stage of disease.[30] In addition, our data reported location of ulcer in the stomach, duodenum and jejunum. The incidence of gastric cancer is significantly low in duodenal ulcers.[13] Low malignancy rates reported by our institution may be attributed due to different

patient demographics, high public awareness for helicobacter pylori infection with increased willingness for screening programs, and liberal use of oesophagogastroduodenoscopy in patients with epigastric pain symptoms. In local context, majority of gastric cancers are identified through oesophagogastroduodenoscopy done for evaluation of patients with epigastric pain, constitutional symptoms and anaemia.

13. Hansson LE, Nyrén O, Hsing AW, Bergström R, Josefsson S, Chow WH, Fraumeni Jr JF, Adami HO. The risk of stomach cancer in patients with gastric or duodenal ulcer disease. New England Journal of Medicine. 1996 Jul 25;335(4):242-9.

28. Hodnett RM, Gonzalez FE, Lee WC, Nance FC, Deboisblanc RE. The need for definitive therapy in the management of perforated gastric ulcers. Review of 202 cases. Annals of Surgery. 1989 Jan;209(1):36.

29. Roviello F, Rossi S, Marrelli D, et al. Perforated gastric carcinoma: a report of 10 cases and review of the literature. World journal of surgical oncology. 2006;4(1):19.

30. Kotan C, Sumer A, Baser M, et al. An analysis of 13 patients with perforated gastric carcinoma: A surgeon's nightmare? World J Emerg Surg. 2008;3:17.

31. Teng TZJ, Sudharsan M, Yau JWK, Tan W, Shelat VG. Helicobacter pylori knowledge and perception among multi-ethnic Asians. Helicobacter. 2021 Jun;26(3);e12794.

Comment 8. Do you test peritoneal fluid and what about fungus and do you give antifungals?

Reply: Yes, peritoneal fluid is sent for fluid culture, but however at surgeon’s discretion, such as signs of infection. We do not routinely give anti-fungals for perforated peptic ulcer. We have included this in our methodology: Peritoneal fluid is sent for fluid culture at discretion of the operating surgeon.

We have also included the following in discussion section: In our opinion, mortality outcomes are not contributed by policy of not-prescribing antifungal therapy routinely.[41]

Comment 9. Does your unit have endoscopic clipping available? Any experience to generate discussion on this.

Reply: Over-the-scope clipping is available in our center. However, this is rarely used for perforated peptic ulcers in our institution. Perforated peptic ulcer remains a surgical emergency in view of propensity for deterioration and risk of haemodynamic instability. While there has been reports on endoscopic management of perforated peptic ulcer,[1] the WSES 2020 guidelines has suggested to avoid the use of endoscopic management in view of the lack of literature and requires further validation.[2] In our opinion, more data is necessary and sutureless repair techniques should be performed as a part of clinical research and should not be considered a standard to be adopted in routine clinical practice.

We have added the following in method section - Sutureless repair was not used in view of the lack of high-quality generalizable evidence.

1. Bergstrom M, Arroyo Vazquez JA, Park PO. Self-expandable metal stents as a new treatment option for perforated duodenal ulcer. Endoscopy. 2013;45:222–5.

2. Tarasconi, A., Coccolini, F., Biffl, W.L. et al. Perforated and bleeding peptic ulcer: WSES guidelines. World J Emerg Surg 15, 3 (2020). https://doi.org/10.1186/s13017-019-0283-9

Comment 10. Overall i feel the data is well presented and you have included limitations like not reporting on pneumonia and urinary or wound infections - so i accept it. If available, such data would be good to have.

Reply: Thank you for the kind compliments. Unfortunately, we do not have data on morbidity on pneumonia, urinary or wound infections following surgery. No edits are made in the manuscript.

Reviewer 2

The authors of this manuscript present an extensive retrospective case series profiling repair of peptic ulcer over a >12 year period while evaluating the relationship between size of the ulcer and leak rate. The center of study is clearly a high volume center, as the case volume is nearly 5 ulcers per month. While the data presented here do contribute some additional knowledge to the topic of perforated ulcer, the results are lacking some important information and the paper does not conclusively address the conclusions as stated in the final paragraph. The manuscript could be improved with addressing several major issues. Some specific comments include:

Comment 1: There are additional characteristics of the patients and ulcers that are relevant but not included. Specifically, ulcer location (gastric/duodenal) is not described even though this is known to be relevant to leak rate.

Reply: Thank you for this question. We agree this information is important and we have included this in **Table 2.** Location of ulcer is as follows: (1) stomach (n=420/690 (60.9%)), (2) duodenum (n=265/690 (38.4%)) and (3) jejunum (n=5/690 (0.7%)).

Comment 2: Can the authors please clarify that omental patch repair was the only method of repair included in this series? For instance, were any of these ulcers closed with primary repair first, then covered with an omental patch on top to buttress the repair? Or was this entirely ulcers that were not primarily repaired and only treated with omental patch?

Reply: This is a very good point and it deserves some clarification of technique. Primary repair first and omental patch on top to buttress would be defined as Cellan-Jones repair. Only omental patch with placement of knots over the patch would be defined as Graham's patch repair. Locally, decision is left at surgeon's discretion; with almost every surgeon option for

Graham's patch in open surgery and Cellan-Jones repair in laparoscopic surgery. Our unit typically does a 3-port laparoscopic repair, and it is relatively difficult to keep the omentum in position while performing intra-corporeal suturing. Further, Graham's patch requires that suture material is left in-situ, until patch is placed over the ulcer defect and then, all knots are tied later. During laparoscopic surgery, this leads to "suture traffic" in the abdominal cavity and could compromise the integrity of accurate knot placements. We have added this in method section: Choice of omental patch repair alone versus primary repair with omental patch buttress was left to surgeon's discretion. Almost all patients managed with open laparotomy undergo omental patch repair alone without primary closure of ulcer i.e. Graham's patch repair. In majority of instances of laparoscopic PPU repair, the perforation was first suture closed and then omental patch was placed as a buttress i.e. Cellan-Jones repair. Our unit typically does a 3-port laparoscopy, and it is relatively difficult to keep the omentum in position while performing intra-corporeal suturing. Further, Graham's patch requires that suture material is left in-situ until the omental patch is placed over the ulcer defect, with subsequent tying of knots. During laparoscopic surgery, this leads to "suture traffic" in the abdominal cavity and could compromise the precision of knotting.

Comment 3: The rate of laparoscopic repair is noted only in passing in the manuscript, and is not able to be analyzed as an independent risk factor for leak, but the discussion contains a significant amount of direction discussing laparoscopic repair. This seems only peripherally relevant to the main point of the paper. Would edit this for discussion most relevant to the data being presented.

Reply: Thank you for the suggestion. The unit experience in laparoscopic surgery is evolving and thus, sample size is small. Increasingly we are adopting laparoscopic approach, and thus

we believe some discussion is warranted. We have removed the emphasis on laparoscopy by re-organising the discussion.

Comment 4: The study would be greatly enhanced by stratifying additional outcomes by ulcer size as well (malignancy, mortality, etc). In the discussion, the authors seem to (though not explicitly) use their results to compare to studies focusing solely on large or giant ulcers and make the conclusion that gastric resection may have worse outcomes. However, their data taken as a whole includes a majority of smaller ulcers. To more definitively establish a size cutoff for alternative methods of repair, need to consider outcomes in addition to leak rate.

Reply: Thank you for this comment. We have performed additionally analysis to investigate mortality and malignancy. For mortality, we obtained an area under curve of 0.731 (95% CI: 0.66, 0.80). This is newly attached as Figure 1B. At ulcer size cut-off of 25mm, AUC of 0.662 (95% CI 0.409, 0.914) was obtained when ulcer size was used to predict incidence of malignancy, which indicates poor performance.

We have added the following in statistical analysis part of method section:

ROC was also performed to evaluate if ulcer size predicted mortality and malignancy.

We have added the following in method section:

ROC analysis correlating ulcer size with mortality yielded an AUC of 0.731 (95% CI: 0.66, 0.80) indicating fair performance (Figure 1B). At 25 mm ulcer size cut off, incidence of mortality was 21.7% and 6.9% for ulcer size ≥25 mm and <25 mm respectively, with sensitivity of 9.8%, specificity of 97.2%, positive LR of 3.48 and negative LR of 0.93 (Table 5). We also additionally performed ROC analysis correlating ulcer size with malignancy, yielding AUC of 0.662 (95% CI 0.409, 0.914), indicating poor performance.

We have added the following in discussion section:

The use of ulcer size cut-off of 25 mm is however, not a good predictor of mortality, with AUC of 0.731 indicating fair performance. A positive LR of above 10 is considered to provide strong evidence to predict risk;[27] we only obtained positive LR of 3.48. We propose that ulcer size of ≥25 mm should be used to predict risk of leak, but not 30-day mortality. In our opinion, mortality risk in patients with sepsis is also determined by underlying patient comorbidity (e.g. diabetes mellitus), and thus independent of ulcer size.[36]

Comment 5: This is a significant amount of ulcers repaired by simple patch repair. How many additional patients were identified and excluded from analysis due to other types of repairs, such as gastric resection, pyloric diversion, etc?

Reply: This is a large 12-year series of admissions to our 1,700 bed tertiary institute, hence the large number of ulcer repair. Omental patch repair is the standard treatment for perforated peptic ulcer in our institute. Management of perforated peptic ulcer in our institution is broadly categorized into omental patch repair and gastrectomy. Serosal patch repair and ulcerectomy and not commonly performed and hence are not included. There were 75 patients who underwent gastrectomy, 2 patients who underwent serosal patch repair and 3 patients who underwent ulcerectomy with pyloric diversion. We have added this in method section: Patients who were managed non-operatively, had undergone alternative modalities of surgery (e.g. serosal patch repair (n=2), ulcerectomy with pyloric diversion (n=3) or gastrectomy (n=75), or who had a perforation of other organs were excluded.

To add, we have reported our experience of gastric resections, and overall estimated 10% of PPU patients are managed with gastric resection in our institution.[10]

10. Seow J, Lim Y, Shelat V. Low serum albumin may predict the need for gastric resection in patients with perforated peptic ulcer. European Journal of Trauma and Emergency Surgery. 2017;43(3):293-298.

Comment 6: In the discussion, do not need the specifics of a power analysis of a proposed study. This is distracting. Can report a possible future study and patients needed, but other details should be removed.

Reply: Thank you for this suggestion. We felt it was essential to account for surgeon's preference as an important determinant of choice of repair and this should be factored in a RCT proposal. We have removed this along with dropout rate. Now the statement reads as - We estimate that such a trial will need to enrol 250 patients in each arm to find a 10% difference in comprehensive complication index with 80% power, two-sided alpha of 5%.

Comment 7: There are several references in the paper to an operating surgeon calling another surgeon with more experience for help. However, there is no data presented to support this suggestion, and I am unfamiliar with any other studies in the literature that support that older or more experienced surgeons have decreased rate of leak or other outcomes.

Reply: Thank you for raising this point. We agree that there is no literature thus far documenting the decreased risk of leak with experience. However, it is known that laparoscopic surgery has a learning curve across all types of surgery. We raised the issue of experience regarding the use of laparoscopic omental patch repair, specifically this statement: Large ulcers should not be considered for laparoscopic omental patch repair by trainees or less experienced surgeons due to already higher rates of a leak.

A study by Lunevicius et al in 2005 on 62 patients who underwent laparoscopic repair of perforated peptic ulcer examined the impact of surgeon experience on leak rates.[1] They failed

to demonstrate a difference in leak rate, but showed high rates of open conversion with lesser experience (1.8±2.3 cases versus 3.9±2.9 cases in successful laparoscopic repair, p=0.039). The authors suggested a learning curve of ten cases.

We agree that this is a peripheral discussion and hence, we have re-arranged the order of our discussion on the impact of a learning curve, especially for laparoscopic omental patch repair. In our experience, calling for help may be considered in instances of dilemma if patch repair is safe or gastric resection is warranted. Further, gastric resection in patients with sepsis and organ dysfunction has its own morbidity risk, and thus patient deserves the best possible 'first chance" and presence of more senior team member is in keeping with good clinical practice. The senior surgeon is an advocate to resident trainees that "when in doubt, please shout out loud" This is aligned to deontological principles as applied to surgical ethics where actions are material rather than mere consequences of actions. Further, it is the duty of senior doctors to ensure junior staff doesn't perceive barriers to seek help.

Nonetheless, our data does not support that experience reduces leak rates and thus, we have deleted – "decision to call for surgeons with more technical expertise" – from concluding remark.

1. Lunevicius R, Morkevicius M. Risk factors influencing the early outcome results after laparoscopic repair of perforated duodenal ulcer and their predictive value. Langenbeck's archives of surgery. 2005 Sep;390(5):413-20.

Comment 8: On the description of baseline characteristics, perforation seen on CT scan is listed as 322 patients but 98.8%, which does not compute with an n=690. Please clarify.

Reply: Thank you for pointing out this. The index modality of imaging in patients with acute abdomen remains erect chest X ray. If pneumoperitoenum is detected on chest X ray, then a

CT scan is not warranted in most patients. Thus CT scan was only performed in 326 patients. We have clarified this the footnote for Table 1: *Value in parenthesis is expressed as percentage of patients who had computed tomography scan (n=326)

Comment 9: The leak is determined by drainage character or confirmed at operation in this study. Were drains used on every patient, or were there some patients that did not have surgical drains placed during the original operation? Is there any difference in leak rate between patients with or without surgical drains? Was any postoperative imaging used to monitor for leaks?

Reply: All patients had routine drain placement intra-operatively. Hence, we are unable to comment on difference in leak rate between patients with or without drain. Post-operative imaging was used to detect a leak in patients where drain effluent was non-bilious. In patients with bilious drain effluent, CT scan imaging was still performed to check for extent of peritoneal contamination and determine if additional percutaneous drain insertion was warranted. We have included this in the method section:

In patients with deviation from expected recovery path, as for example, pyrexia, haemodynamic instability, or evolving abdominal symptoms or signs, an urgent CT scan of the abdomen and pelvis, with oral and intravenous contrast was performed to diagnose leak as well as guide the management. In patients with obvious bilious fluid or gastrointestinal contents in the drain tube, a CT scan was still performed to guide further management, as for example if placement of image guided percutaneous drains was warranted for source control.

Comment 10: The use of PPV and NPV would typically be used to refer to a test result, and this would seem to be more clearly referred to as a rate of leak by ulcer size. Consider

revising table 4 to be more clear in the message the authors are trying to convey with this information.

Reply: Thank you for the suggestion. We have amended table 4 accordingly and included sensitivity, specificity, leak rate and likelihood ratios. Likelihood ratio allows us to compare the risk of leak for patients with ulcer size more than a particular value compared to less than that value, without having to depend on prevalence. Likelihood ratio are also used for non "test results".[1]

1. Deeks J J, Altman D G. Diagnostic tests 4: likelihood ratios BMJ 2004; 329 :168 doi:10.1136/bmj.329.7458.168

Comment 11: Finally, I would mention that multiple times in the manuscript, the authors note that ulcer size has been related to leak rate in other studies and say that their findings are not novel or unexpected. If this is the case, why would the study be worth publishing? Would remove statements that diminish the work included here. It is important to acknowledge other studies that report findings similar to those presented, but it is important to demonstrate why the work here is important and how it may affect further studies or clinical outcomes. Would adjust the study to more comprehensively evaluate an appropriate cutoff for ulcer size to not only include leak rate, but rate of malignancy, mortality, and other complications to more definitively demonstrate a cutoff at which alternative methods of surgical management should be considered.

Reply: Thank you for the suggestion. We have rephrased our abstract and discussion in entirety to emphasises on the importance of our study. In addition, we have included additional data analysis on risk factors for mortality as well as malignancy.

Reviewer 3

1. It's an excellent article. But the article did not mention how long it takes when the patient presented at hospital and was sent to receive the operation. It will be perfect if this is discussed in the article.

Reply: Thank you for the comments. We have included the following in our methodology:

Our institution triages the urgency of surgery using a central anaesthetist led triage system of P0, P1, P2, P3A, P3B, and P4 categories. P0 indicates life-threatening disease which requires immediate surgery, while P4 indicates stable disease which does not require urgent surgery. Time to surgery for P0, P1, P2, P3A, P3B and P4 are as follows: immediate, within 1 hour, within 4 hours, within 8 hours, within 12 hours and within 24 hours, respectively. All cases of PPU are triaged as P2 by default, with variability allowances for reasonable clinical judgment in selected patients.

Unfortunately, we do not have data on the median time to operation. We agree that this is an interesting point for discussion as delay to surgery has been associated with higher mortality. We have added this in the discussion:

Our series also reported low 30-day mortality of 7.4% which is consistent with existing literature ranging 1.3% to 20%.[9,32] Delay in surgery has been associated with higher mortality and has been postulated to be due to the extent of peritoneal contamination.[33] A large nationwide cohort study by Boyd-Carson et al in 2020 on 3809 patients with perforated peptic ulcer who underwent emergency laparotomy within 24 hours showed an adjusted 4% increase in mortality per every hour delay to surgery, and an adjusted 6% increase in mortality per every hour delay in patients with shock.[34] Median time to surgery from admission in their study was 7.5 hours (interquartile range 5-11.6 hours).[34] Svanes et al. reported marked delay

of ≥12 hours to surgery resulted in higher mortality (22.8% vs 5.9%, p<0.001), post-operative complications (48.6% vs 24.6%, p<0.001) and prolonged stay > 14 days (33.8% vs 20.3%, p=0.001) in ≥50 years old patients.[35] Even though we did not collect data on the time to surgery, our institution triages PPU as P2 category (to be done within 4 hours) as a default. Thus, majority of our PPU patients are operated within 12 hours of diagnosis. This may explain our low mortality rate.

9. Chung KT, Shelat VG. Perforated peptic ulcer-an update. World journal of gastrointestinal surgery. 2017;9(1):1.

32. Boey J, Choi SK, Poon A, et al. Risk stratification in perforated duodenal ulcers. A prospective validation of predictive factors. Annals of surgery. 1987;205(1):22-26.

33. Boey J, Wong J, Ong GB. Bacteria and septic complications in patients with perforated duodenal ulcers. The American Journal of Surgery. 1982;143(5):635-639.

34. Boyd-Carson H, Doleman B, Cromwell D, et al. Delay in Source Control in Perforated Peptic Ulcer Leads to 6% Increased Risk of Death Per Hour: A Nationwide Cohort Study. World Journal of Surgery. 2020;44(3):869-875.

35. Svanes C, Lie RT, Svanes K, et al. Adverse effects of delayed treatment for perforated peptic ulcer. Annals of surgery. 1994;220(2):168-175.

Author Self- edits

1. We have introduced short form OPL for omental patch repair leak

2. We have introduced short form LR in table 4 and 5 for Likelihood ratio

2nd Editorial decision
07-Nov-2021

Ref.: Ms. No. JCTRes-D-21-00160R1
Omental patch repair of large perforated peptic ulcers ≥25mm is associated with higher leak rate
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers:

Reviewer #1: Thanks for detailed explanations and edits.
It looks better. I am okay with it.

Reviewer #2: The authors have addressed all of the comments from previous review. I believe that this manuscript is appropriate for publication at this time.