PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Factors associated with failure of enhanced recovery protocol in patients undergoing major hepatobiliary and pancreatic surgery: a retrospective cohort study
AUTHORS	Lee, Anna; Chiu, Chun Hung; Cho, Mui Wai Amy; Gomersall, Charles; Lee, Kit Fai; Cheung, Yue Sun; Lai, Paul Bo San

VERSION 1 - REVIEW

REVIEWER	Ross Kerridge Associate Professor, Anaesthesia & Perioperative Medicine John Hunter Hospital Faculty of Health and Medicine University of Newcastle Newcastle, NSW Australia
REVIEW RETURNED	05-May-2014

GENERAL COMMENTS	Access and appropriate utilisation of Intensive Care resources for elective and emergency surgical patients is currently an issue of concern internationally. This has been emphasised by the findings of somewhat unexpectedly high morbidity and mortality following surgery, as demonstrated in the REASON and EUSOS studies. In order to optimise ICU resource utilisation, there is a need to better understand which patients will benefit from planned ('preventive') intensive care unit resources to be used postoperatively. There is also a need to better predict those patients who are likely to develop complications and need prolonged intensive care stay, or readmission to ICU, postoperatively. The cohort described is at a single centre, and is not particularly large, however is large enough to produce some interesting findings. It must be noted that: 1. The patient group is “young” (mean age 58) and appears to be predominately “fit” (ASA 1 and 2). 2. Although the hospital does not have a surgical high dependency unit, there appears to be good access to intensive care. I note that 48.5% of patients went to intensive care post-operatively, as a planned ICU admission. In the EUSOS study, access to ICU postoperatively was considered to be a major factor affecting patient outcome. 3. There were no deaths in the cohort. This is very a very notable achievement, and perhaps emphasises the benefits of ICU access, and the benefits of planned care - the goal of an ERAS program. 4. There is no information about the incidence of obesity (e.g. BMI)

	of the patient group, nor the incidence of diabetes. The cohort demonstrates that “failure” of ERAS (as demonstrated by longer ICU stay as well as longer hospital stay) are predicted by development of postoperative complications. Failures are not predicted by the magnitude of surgery. This has been shown in other studies such as REASON. Of particular interest, is that this study suggests that preoperative raised transaminases and smoking are independent predictors of ICU utilisation. Although unsurprising, this is useful information to help predict ICU utilisation. The importance of liver inflammation as a perioperative risk needs further study in larger populations. It would be useful if the smoking data was analysed as a continuous variable based on cotinine concentrations, rather than a categorical variable based on smoking in the last six weeks preoperatively. The smoking result emphasises the need for increased smoking cessation efforts preoperatively, but a result linked to cotinine concentration would be much more interesting. If the cotinine values could be added, and the data reanalysed using this data as a continuous variable, it would add further interest to the paper. Is data about obesity and diabetes available?

REVIEWER	Coolsen, Marielle University Hospital Maastricht (MUMC+) The Netherlands
REVIEW RETURNED	05-May-2014

GENERAL COMMENTS	The authors present a cohort study of patients undergoing HPB surgery in an ERAS programme in which they try to determine the incidence of failure of an ERAS programme for HPB surgery and identify risk factors that are associated with this failure. The authors conclude that smokers, patients with a high risk of postoperative morbidity or patients with a high preoperative level of alanine transaminase/glutamic-pyruvic transaminase are likely to fail the ERAS program. This is an interesting article since it is one of the first articles to assess factors that are associated with failure of an ERAS program in HPB surgery. However, important information about the ERAS programmes used in this study is missing (see questions below). Furthermore, the study design is not completely clear to me. The authors use a composite endpoint to define failure of an ERAS programme. However, reporting only this composite endpoint (which is probably not validated) does not suffice. At least information should be provided also on adherence to different elements of the ERAS programme and the individual elements of the composite endpoint should be described more in detail.

	Major comments: 1. Could the authors elaborate on the choice of outcome measures? For instance, why consider readmission as a direct and complete failure of an ERAS programme? Reasons for the readmissions should be reported. 2. Did the authors validate the selected composite endpoint? It is not clear whether the study was powered on this composite endpoint or not. 3. Why did the authors choose not to provide information about the adherence to the different elements of the ERAS programme? The occurrence of a postoperative complication does not necessarily mean the whole ERAS programme has failed. There should at least be some information on for instance adherence to nutritional targets, early mobilisation and drain/tube management. 4. Why did the authors determine postoperative morbidity only on day 3? What about complications that occur after day 3? 5. The study population is very heterogenous. It is difficult to compare patients undergoing pancreaticoduodenectomy with distal pancreatectomy and open and laparoscopic liver surgery. Both patient and complication management in these groups vary too much to be able to draw general conclusions. It would be better to consider these groups separately. 6. The authors did not describe the ERAS protocols they used for the different patient groups. For sure, there are common elements across the different groups but there must exist a specific difference in ERAS management between a patient undergoing Whipple surgery and a patient undergoing laparoscopic liver surgery. I would like to see a more detailed explanation of this (a description of the different ERAS programs could for instance be presented in an extra table or as supplementary material). 7. I have serious doubts whether the authors are really performing ERAS care. For instance, the use of nasogastric tubes for 3 days after Whipple surgery cannot really be considered ERAS practice. The ERAS guidelines for pancreatico-duodenectomy state that NG tubes should not be used routinely and patients should be allowed a normal diet after surgery without restrictions (Lassen K. et al. Clin Nutr. 2012 Dec;31(6):817-30). Could the authors elaborate on this? I also did not find any information regarding nutritional management. This is an essential and basic element of any ERAS program and should be included. 8. Patients did not receive epidural analgesia (which is the recommended because studies show better pain relief and fewer respiratory complications). Instead PCA was used. What was analgesic agent was used for PCA? NB: The use of morphine is discouraged. 9. Early mobilization is not defined. Was it structured, under guidance of a physiotherapist? From which day after surgery? 10. How was drain management for patients undergoing Whipple surgery? Did the patients undergoing liver surgery receive a prophylactic intra-abdominal drain? 11. The methods section states that patients were recruited from a larger cohort study of 736 patients to examine the

	association between **passive** smoking and risk of perioperative respiratory complications and postoperative morbidity. The result section reports on **active** smokers. What should it be? 12. Table 2: "Any postoperative morbidity" on day 3 was associated with failure of an ERAS programme. Perhaps it would be better to classify complications according to a complication classification system (the Dindo-Clavien classification for instance). I can't imagine a wound infection has as much impact on failure of an ERAS programme than a reoperation for a pancreatic fistula. Minor comments: 1. Table 1: what is defined as major and what is defined as ultramajor surgery? 2. How many patients were extubated directly after surgery? 3. How many patients had to undergo a re-intervention? For instance CT-guided drainage of collections/abscesses? 4. Make sure that the English language in the manuscript is checked by a native English speaking person qualified in the scientific field.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Ross Kerridge

Institution and Country Associate Professor,

Anaesthesia & Perioperative Medicine

John Hunter Hospital

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Please state any competing interests or state 'None declared': None declared

Access and appropriate utilisation of Intensive Care resources for elective and emergency surgical patients is currently an issue of concern internationally. This has been emphasised by the findings of somewhat unexpectedly high morbidity and mortality following surgery, as demonstrated in the REASON and EUSOS studies.

We have read both studies and agree with the above comment.

In order to optimise ICU resource utilisation, there is a need to better understand which patients will benefit from planned ('preventive') intensive care unit resources to be used postoperatively. There is also a need to better predict those patients who are likely to develop complications and need prolonged intensive care stay, or readmission to ICU, postoperatively.

We agree with the above comment and believe that this study provides a better understanding specifically to HBP surgical patients.

The cohort described is at a single centre, and is not particularly large, however is large enough to produce some interesting findings.

It must be noted that:

1. The patient group is “young” (mean age 58) and appears to be predominately “fit” (ASA 1 and 2).

We agree with the above comment that the patient group is young compared to those in the REASON study and have added text about ASA I and 2 in the Discussion (first paragraph) to highlight this finding.

2. Although the hospital does not have a surgical high dependency unit, there appears to be good access to intensive care. I note that 48.5% of patients went to intensive care post-operatively, as a planned ICU admission. In the EUSOS study, access to ICU postoperatively was considered to be a major factor affecting patient outcome.

We agree with the above comment and have made reference to the EUSOS study about access to postoperative ICU affecting patient outcome in the discussion, 2nd paragraph.

3. There were no deaths in the cohort. This is very a very notable achievement, and perhaps emphasises the benefits of ICU access, and the benefits of planned care - the goal of an ERAS program.

We have expanded the discussion on low death rate in the discussion (1st paragraph) by inserting the text “This may be due to the majority of our patients (86%) classified as American Society of Anesthesiologists’ physical status grades I and II, benefits of planned bundles of care in the ERAS program or good access to postoperative ICU care.”

4. There is no information about the incidence of obesity (e.g. BMI) of the patient group, nor the incidence of diabetes.

We did not collect BMI or diabetes in the main study on the effects of passive smoking on risk of perioperative respiratory complications and postoperative morbidities from which this subcohort was taken retrospectively. We note that diabetes and obesity were not significant factors in the adjusted odds ratio for 30-day mortality in the REASON Study.

The cohort demonstrates that “failure” of ERAS (as demonstrated by longer ICU stay as well as longer hospital stay) are predicted by development of postoperative complications. Failures are not predicted by the magnitude of surgery. This has been shown in other studies such as REASON. Of particular interest, is that this study suggests that preoperative raised transaminases and smoking are independent predictors of ICU utilisation. Although unsurprising, this is useful information to help predict ICU utilisation.

With regarding to the magnitude of surgery as a risk factor for ERAS failure, we did not find an association. It is difficult to compare our findings to other studies, as both the REASON and EUSOS studies essentially measured mortality as the outcome.

The importance of liver inflammation as a perioperative risk needs further study in larger populations.

We agree and note that serum glutamic-oxaloacetic transaminases (SGOT)>40 was associated with mortality at 24-h and 30-day in 815,077 elective non-cardiac surgery in USA (Bishop et al. Factors associated with unanticipated day of surgery deaths in Department of Veterans Affairs Hospitals. Anesth Analg 2008;107:1924-35). We have not included this text in our manuscript as our ALT/GPT is not the same as SGOT, and the outcomes are different.

It would be useful if the smoking data was analysed as a continuous variable based on cotinine concentrations, rather than a categorical variable based on smoking in the last six weeks preoperatively. The smoking result emphasises the need for increased smoking cessation efforts preoperatively, but a result linked to cotinine concentration would be much more interesting. If the cotinine values could be added, and the data reanalysed using this data as a continuous variable, it would add further interest to the paper.

We have reanalyzed the data using urinary cotinine concentration as a sensitivity analysis to Table 3. The results are shown in Table 4 and supplementary text has been added to the manuscript to help the reader interpret the risk of failure with adjusted cotinine concentrations at 50, 500 and 1500 ng/ml.

Is data about obesity and diabetes available?

We did not collect BMI or diabetes in the main study on the effects of passive smoking on risk of perioperative respiratory complications and postoperative morbidities from which this subcohort was taken retrospectively.

Reviewer: 2

Reviewer Name MME Coolsen

Institution and Country University Hospital Maastricht (MUMC+)

The Netherlands

Please state any competing interests or state 'None declared': none declared.

Comments to the authors:

The authors present a cohort study of patients undergoing HPB surgery in an ERAS programme in which they try to determine the incidence of failure of an ERAS programme for HPB surgery and identify risk factors that are associated with this failure. The authors conclude that smokers, patients with a high risk of postoperative morbidity or patients with a high preoperative level of alanine transaminase/glutamic-pyruvic transaminase are likely to fail the ERAS program.

This is an interesting article since it is one of the first articles to assess factors that are associated with failure of an ERAS program in HPB surgery. However, important information about the ERAS programmes used in this study is missing (see questions below). Furthermore, the study design is not completely clear to me. The authors use a composite endpoint to define failure of an ERAS programme. However, reporting only this composite endpoint (which is probably not validated) does not suffice. At least information should be provided also on adherence to different elements of the ERAS programme and the individual elements of the composite endpoint should be described more in detail.

We have made the study design clearer in the revised title and in the methods section. We have reported on the incidence of each component used in the composite endpoint. As requested, we have provided further details about the reasons for hospital readmission in the Results (1st paragraph). The main advantage for using composite endpoint over modeling the association between risk factors and each individual outcome is to increase statistical power. We also feel that failure of an ERAS program is not sufficiently characterized by only one outcome. In the revised manuscript, we have described our HBP ERAS program in more detail in response to the questions raised by this reviewer.

Major comments:

1. Could the authors elaborate on the choice of outcome measures? For instance, why consider readmission as a direct and complete failure of an ERAS programme? Reasons for the readmissions should be reported.

We have already described the reasons for the choice of outcome measures in the original manuscript. Nevertheless, we have expanded this statement in the methods section to read "These events were chosen as markers of slow recovery and are common quality of care indicators". The reasons for readmissions are now reported in the revised manuscript in the Results section (1st paragraph).

2. Did the authors validate the selected composite endpoint? It is not clear whether the study was powered on this composite endpoint or not.

As this was an exploratory analysis on a retrospective cohort study, we chose to have an adequate sample size for developing a risk model with a fair discrimination property. We did not formally 'validate' the composite endpoint but we were mindful that the chosen individual components of the

composite outcome were at least in the same direction for risk of ERAS failure. Statistical methods for composite outcomes are relatively new and complex.

3. Why did the authors choose not to provide information about the adherence to the different elements of the ERAS programme? The occurrence of a postoperative complication does not necessarily mean the whole ERAS programme has failed. There should at least be some information on for instance adherence to nutritional targets, early mobilisation and drain/tube management.

Our focus is not on the noncompliance with various elements of the ERAS program for defining 'failure'. As discussed, "better patient care and outcome can be achieved regardless of the number, the combination, the type, and the strength of evidence of the individual ERAS component.[33,34]"

The adherence to nutritional targets, early mobilization and drain/tube management were largely affected by the occurrence of complications, which also explains why postoperative complication related to failure of ERAS program. Postoperative morbidities were associated with longer duration of hospital stay (Davies et al. Measuring outcomes after major abdominal surgery during hospitalization: reliability and validity of the Postoperative Morbidity Survey. Periop Med 2013;2:1) and increased risk of hospital readmission (Lucas et al. The timing of complications impacts risk of readmission after hepatopancreatobiliary surgery. Surgery 2014;155:945-53).

In the revised methods section and Table 1, we describe nutritional targets, early mobilization and drain/tube management in more detail.

4. Why did the authors determine postoperative morbidity only on day 3? What about complications that occur after day 3?

The validated and reliable Postoperative Morbidity Survey tool has the highest inter-rater reliability on Day 3 (Davies et al. Measuring outcomes after major abdominal surgery during hospitalization: reliability and validity of the Postoperative Morbidity Survey. Periop Med 2013;2:1). We have already acknowledged that a study limitation was that we did not collect late postoperative complications occurring after the third day after surgery.

5. The study population is very heterogenous. It is difficult to compare patients undergoing pancreaticoduodenectomy with distal pancreatectomy and open and laparoscopic liver surgery. Both patient and complication management in these groups vary too much to be able to draw general conclusions. It would be better to consider these groups separately.

We agree that the surgical population is very heterogenous. However, the small sample size in the pancreatic surgery was too small for risk modelling to be useful.

6. The authors did not describe the ERAS protocols they used for the different patient groups. For sure, there are common elements across the different groups but there must exist a specific difference in ERAS management between a patient undergoing Whipple surgery and a patient undergoing laparoscopic liver surgery. I would like to see a more detailed explanation of this (a

description of the different ERAS programs could for instance be presented in an extra table or as supplementary material).

In the revised manuscript, we describe the ERAS protocol used for the two different patient populations in the Methods and in Table 1. Within the same surgical category, we accept fine adjustment to each component of ERAS. For example, patients undergoing laparoscopic liver resection can resume normal diet on the second postoperative day and be discharged on the third day after surgery.

7. I have serious doubts whether the authors are really performing ERAS care. For instance, the use of nasogastric tubes for 3 days after Whipple surgery cannot really be considered ERAS practice. The ERAS guidelines for pancreatico-duodenectomy state that NG tubes should not be used routinely and patients should be allowed a normal diet after surgery without restrictions (Lassen K. et al. Clin Nutr. 2012 Dec;31(6):817-30). Could the authors elaborate on this? I also did not find any information regarding nutritional management. This is an essential and basic element of any ERAS program and should be included.

See our response to above question. There are variations in the multimodal elements of ERAS programs around the world (Hall et al. Ann R Coll Surg Engl 2012;94:318-26). Our centre adopts pylorus-preserving pancreatico-duodenectomy, which is associated with a higher rate of gastric outlet obstruction.

The use of nasogastric tube in Whipple's operation should be judicious but is not absolutely contraindicated. In our experience, delayed gastric emptying occurs in up to 30% of patients. Thus we were more cautious about the occurrence of such complication, so we kept the nasogastric tube in for at least three days after surgery to exclude such complication.

8. Patients did not receive epidural analgesia (which is the recommended because studies show better pain relief and fewer respiratory complications). Instead PCA was used. What was analgesic agent was used for PCA? NB: The use of morphine is discouraged.

We did not routinely used epidural anaesthesia/analgesia because of concerns about postoperative coagulopathy. In the revised manuscript, we have added a reference by Shontz et al. Reg Anesth Pain Med 2009;34:308-311 where they found the high prevalence of coagulopathy (47%) in patients receiving epidural analgesia for hepatic surgery. Nevertheless, epidural analgesia was restricted to those patients who specifically requested for it because of pain concerns or had preoperative impaired respiratory function.

Our patients are generally satisfied with the quality of pain relief provided by IV PCA. PCA morphine was used at our institution. This is now clarified in the revised manuscript under Methods.

9. Early mobilization is not defined. Was it structured, under guidance of a physiotherapist? From which day after surgery?

Our patients were mobilized first day after surgery by sitting out of bed. Walking exercises were initiated by the physiotherapists and nurses.

10. How was drain management for patients undergoing Whipple surgery? Did the patients undergoing liver surgery receive a prophylactic intra-abdominal drain?

For liver surgery, the decision to use prophylactic intra-abdominal drain was left to the operating surgeons. The drain was not placed after liver resection unless there was a high chance of postoperative ascites or bile leak after major hepatectomy in patients with significant portal hypertension or after hepatectomy for hepatolithiasis.

In patients undergoing Whipple's operation, the insertion of abdominal drains was routine. These drains were kept for at least four days and were removed if there were no clinical features (ie. low serum and drain fluid amylase level, absence of bile or pancreatic juice from the drain output) suggestive of pancreatic fistula or bile leak.

11. The methods section states that patients were recruited from a larger cohort study of 736 patients to examine the association between passive smoking and risk of perioperative respiratory complications and postoperative morbidity. The result section reports on active smokers. What should it be?

We have kept the same definition for current smokers in this and the larger cohort study as "Current smoking was defined as no smoking cessation within 2 months before surgery or the patient had an adjusted urinary cotinine concentration >550 ng/mL within 48 hours before surgery.[10]" In the revised manuscript, we have performed a sensitivity analysis on the risk model using adjusted urinary cotinine concentration as a continuous independent variable as requested by the other reviewer and the results are shown in Table 4.

12. Table 2: "Any postoperative morbidity" on day 3 was associated with failure of an ERAS programme. Perhaps it would be better to classify complications according to a complication classification system (the Dindo-Clavien classification for instance). I can't imagine a wound infection has as much impact on failure of an ERAS programme than a reoperation for a pancreatic fistula.

The Postoperative Morbidity Survey (POMS) tool is a valid and reliable instrument in terms of inter-rater reliability, face validity, discriminant construct validity, convergent validity and clinical acceptability for identifying postoperative morbidity. The POMS measurement was collected prospectively in the main study examining the effect of passive smoking on perioperative respiratory complications and postoperative morbidities. The Dindo-Clavien classification is widely used by surgeons to classify 'severity' of surgical complications based on the type of therapy used to treat the complication but we were unaware of the psychometric properties associated with this classification system.

Minor comments:

1. Table 1: what is defined as major and what is defined as ultramajor surgery?

The extent of hepatobiliary and pancreatic surgery was classified by the surgeons using the criteria according to the Hong Kong Government Gazette (Hong Kong Government. Hong Kong Government Gazette No.13/2003 Special Supplement No.4.Annex IV 2003; D4668-D4704). For example, all Whipple's operation was classified as ultramajor surgery.

2. How many patients were extubated directly after surgery?

All patients were extubated after surgery from data provided in the anaesthetic record.

3. How many patients had to undergo a re-intervention? For instance CT-guided drainage of collections/abscesses?

We do not know how many patients had undergone a re-intervention as we did not collect this data in this study.

4. Make sure that the English language in the manuscript is checked by a native English speaking person qualified in the scientific field.

The first author is a native English speaker who wrote her PhD thesis at the University of New South Wales, Sydney Australia.

VERSION 2 – REVIEW

REVIEWER	Ross Kerridge John Hunter Hospital University of Newcastle Australia
REVIEW RETURNED	19-Jun-2014

GENERAL COMMENTS	I am satisfied that the Authors have addressed the earlier comments from both of the reviewers.

REVIEWER	Coolsen, Marielle Maastricht university hospital (MUMC+), the Netherlands
REVIEW RETURNED	14-Jun-2014

- The reviewer completed the checklist but made no further comments.