BMJ Open

Factors associated with failure of enhanced recovery protocol in patients undergoing major hepatobiliary and pancreatic surgery: a cohort study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005330
Article Type:	Research
Date Submitted by the Author:	24-Mar-2014
Complete List of Authors:	Lee, Anna; The Chinese University of Hong Kong, Anaesthesia and Intensive Care Chiu, Chun Hung; The Chinese University of Hong Kong, Anaesthesia and Intensive Care Cho, Mui Wai Amy; The Chinese University of Hong Kong, Anaesthesia and Intensive Care Gomersall, Charles; The Chinese University of Hong Kong, Anaesthesia and Intensive Care Lee, Kit Fai; The Chinese University of Hong Kong, Division of Hepatobiliary and Pancreatic Surgery Cheung, Yue Sun; The Chinese University of Hong Kong, Division of Hepatobiliary and Pancreatic Surgery Lai, Paul Bo San; The Chinese University of Hong Kong, Division of Hepatobiliary and Pancreatic Surgery
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Health services research, Surgery
Keywords:	Hepatobiliary surgery < SURGERY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Factors associated with failure of enhanced recovery protocol in patients undergoing major hepatobiliary and pancreatic surgery: a cohort study

Anna LEE[1], Chun Hung CHIU[1], Mui Wai Amy CHO[1], Charles David GOMERSALL[1], Kit Fai LEE[2], Yue Sun CHEUNG[2], Paul Bo San LAI[2]

[1] Department of Anaesthesia and Intensive Care, Prince of Wales Hospital, The Chinese University of Hong Kong

[2] Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Prince of Wales Hospital, The Chinese University of Hong Kong

Address for correspondence: Anna Lee, Department of Anaesthesia and Intensive Care, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong

Phone: +852 2632 2735 Fax: +852 2637 2422 Email: annalee@cuhk.edu.hk

Reprints: Reprints will not be available from the authors

Category: Research article

Meeting: Will be presented in part at the combined Royal Australasian College of Surgeons Annual Scientific Congress and the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine Annual Scientific Meeting, in Singapore, 5th-9th May 2014.

MESH terms: Enhanced recovery after surgery; Postoperative care; Liver surgery; Pancreatic surgery; Cohort

Word count: 245 (abstract); 3043 (text)

ABSTRACT

Background: Enhanced recovery after major hepatobiliary and pancreatic (HBP) surgery have been shown to reduce postoperative morbidities, length of hospital stay and costs but compliance with core elements varies considerably among centers. This study examined risk factors associated with failure of enhanced recovery protocol after HBP surgery to identify patients needing additional care to minimize perioperative morbidities and length of stay.

Methods: A cohort of 194 patients undergoing major HBP surgery was followed up for 30 days. The primary outcome was failure of enhanced recovery protocol, which was defined as a composite measure of the following events: intensive care unit (ICU) stay more than 24 hours after surgery, unplanned admission to ICU within 30 days after surgery, hospital readmission, reoperation and mortality.

Results: There were 25 failures of enhanced recovery after HBP surgery (12.9%, 95% CI, 8.5% to 18.4%). After adjusting for elective ICU admission, smokers (RR 2.21, 95% CI, 1.10 to 4.46), high preoperative alanine transaminase/glutamic-pyruvic transaminase (RR 3.55, 1.68 to 7.49) and postoperative morbidities (RR 2.69, 95% CI, 1.30 to 5.56) were associated with failures of enhanced recovery in the generalized estimating equation risk model. Compared to those managed successfully, failures stayed longer in ICU (median 19 *vs.* 25 hours, $P<0.001$) and in hospital for postoperative care (median 7 *vs.* 13 days, $P=0.003$).

Conclusion: Smokers and patients having high preoperative alanine transaminase/glutamic-pyruvic transaminase concentration or have a high risk of postoperative morbidities are likely to fail enhanced recovery protocol in HBP surgery programs.

Strengths and limitations of this study

- This is the first study to identify risk factors associated with the failure of enhanced recovery protocol in major hepatobiliary and pancreatic surgery.
- Instead of using length of hospital stay as an endpoint, failure was defined as a composite measure of slow recovery: length of stay in the intensive care unit (ICU) more than 24 hours after surgery, unplanned admission to ICU within 30 days, readmission to the hospital within 30 days after surgery, reoperation for complications and 30-day mortality
- Smokers (defined by self-reported history and urinary cotinine concentration) and patients having high preoperative alanine transaminase glutamic-pyruvic transaminase concentration or have a high risk of postoperative morbidities are likely to fail clinical pathways in fast-track hepatobiliary and pancreatic surgery.
- We did not consider the compliance rate of individual components of the early recovery after hepatobiliary pancreatic surgery program
- High risk patients at risk of failing enhanced recovery protocols in major hepatobiliary pancreatic surgery may benefit from additional care to minimize perioperative morbidities and length of stay.

INTRODUCTION

Enhanced recovery after major hepatobiliary and pancreatic surgery (ERAHBPS) is a complex intervention that includes many of the following components: patient and family education, no bowel preparation, no preanaesthetic medication, preoperative carbohydrate loading, thromboembolic prophylaxis, antiemetic prophylaxis, epidural analgesia, intraoperative normothermia, prophylactic antibiotics, no systemic opioids, fluid restriction, no surgical drains, no standard postoperative nasogastric tubes, postoperative nutritional care and early mobilization.[1]

Recent systematic reviews[1,2] of several observational studies of ERAHBPS programs suggest that it is safe and feasible. Compared to traditional clinical pathways, fast-track hepatobiliary and pancreatic (HBP) surgery programs have similar risks of readmission, morbidity and mortality[1-3] and reduced the duration of postoperative length of stay and overall hospital cost.[3] However, compliance with core components of enhance recovery after liver surgery program vary between high-volume European centers, with a median adoption of 9 (range 7 to 12) of 22 core elements.[4]

As with all enhanced recovery after surgery (ERAS) programs, a small proportion of patients will fail fast-track HBP surgery and require additional intensive care unit (ICU) resources. Although not all fast-track HBP surgical patients are routinely admitted to ICU after their procedure,[5,6] ICU care after liver resection was associated with a decreased risk in hospital mortality (odds ratio 0.26, 95% CI 0.10 to 0.71) and a reduction in total hospital costs (13%).[7] These results suggest that careful selection of patients for ERAHBPS is crucial for maximizing the efficiency of perioperative care pathways.

Fast-track failure risk models after cardiac surgery have been developed[8] and externally validated[9] to facilitate the planning of perioperative care pathways, but factors associated with failure of enhanced recovery protocol after HBP surgery are unknown. The objectives of this study were to estimate the incidence of and identify the risk factors associated with failure of enhanced recovery protocol after HBP surgery. And with such information, we can identify a subgroup of patients at risk of failure to provide additional care to minimize perioperative morbidities and length of stay.

METHODS

Study cohort

The Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee approved this cohort study of patients undergoing major HBP surgery at the Prince of Wales Hospital in Hong Kong between January 2011 and November 2012 (CRE-2013.181). The patients were from a larger cohort study of 736 consecutive adult patients with preoperative urinary cotinine concentration to examine the association between passive smoking and risk of perioperative respiratory complications and postoperative morbidities.[10] All patients gave written informed consent before surgery. Patients undergoing other types of surgery, unable to give written informed consent, having chronic renal failure, younger than 18 years and urine cotinine samples collected more than 48 h before surgery were excluded.

The types of surgery included were laparoscopic liver resection (nonanatomical wedge resections, or resection of 1 or 2 segments), minor open liver resection (fewer than 3 segments including multiple non-anatomical resections), major open liver resections (3 or more segments), liver resection with biliary reconstruction[11,12] and pancreatic surgery. Pancreatic surgery included Whipple procedure, double bypass (hepaticojejunostomy and gastrojejunostomy in unresectable cancer of the head of pancreas) and distal pancreatectomy.

Typical management

The typical clinical care pathway for HBP surgical patients involved the following: admission to surgical ward one day before surgery, patient education, no preanaesthetic medication, mechanical prophylaxis for deep vein thrombosis, intraoperative prophylactic antibiotics, normothermia during surgery, ICU or surgical ward for first 24 h after surgery, surgical ward, early mobilization and hospital discharge. Patient controlled analgesia was regularly prescribed to patients undergoing open HBP surgery. For pancreatic surgery, abdominal drains and nasogastric tubes were routinely placed and kept in place for at least 2 to 3 days after surgery. The use of epidural anaesthesia is not routine because of concerns about postoperative coagulopathy in patients with cirrhosis of liver.

Although there was no formalized extubation protocol, extubation at the end of liver resection surgery or within 1 h after admission to ICU was expected; for pancreatic surgery where most patients went to ICU, extubation within 4 h was expected. There is no surgical high dependency unit at the Prince of Wales Hospital, Hong Kong.

Outcome Measure

For the purposes of this study, we define failure of enhanced recovery protocol after HBP surgery as a composite measure of the following events: length of ICU stay more than 24 h after surgery, unplanned admission to ICU within 30 days after surgery, readmission to the hospital within 30 days after surgery, reoperation for complications and 30-day mortality. These events were chosen as markers of slow recovery. Unlike previous ERAS studies, we did not chose length of stay as a primary outcome as it has been shown that reductions in length of stay up to a median of 2 days may be related to changes in organization of care and not to the effect of the ERAS program.[13]

We collected patient demographics, smoking status, preoperative urinary cotinine concentration that was adjusted for creatinine level, American Society of Anesthesiologists' Physical Status, Surgical Apgar score,[14] duration of surgery, ICU admission details, APACHE II (severity of illness score in patients admitted to ICU),[15] preoperative liver function tests, indocyanine green test and coagulation tests, and failure events from the hospital electronic Clinical Management System database. The research staff collected postoperative morbidities (pulmonary, infectious, renal, gastrointestinal, cardiovascular, neurological, haematological, wound and severe pain) on the third day after surgery using a reliable and valid Postoperative Morbidity Survey questionnaire.[16] The EQ-5D index, a health-related quality of life using a US set of reference weights, was measured on the third day after surgery[17] as the greatest difference in EQ-5D index between ERAHBPS and standard care occur between postoperative day 2 and 5.[18] 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] The research staff was blinded to the urinary cotinine concentration results.

Statistical Analysis

Continuous data were expressed as mean and standard deviation (SD) or median and interquartile range (IQR). The 95% confidence interval (95% CI) was estimated around the incidence of HBP surgery failure. Appropriate Student t-tests, Mann-Whitney U tests, χ^2 analyses or exact tests were used to compare factors associated with failure of enhanced recovery protocol. To adjust for multiple testing of individual postoperative morbidity events, a Bonferroni correction was used so that the significance criterion was set at $P<0.0063$. There was no missing data.

A generalized estimating equation (GEE) model with a Poisson distribution, log-link function and exchangeable correlation[19] was used to obtain a common-effect relative risk (RR) of failure of enhanced recovery protocol after HBP surgery. This GEE model was more appropriate for analysis of composite measures and assumes that there is a single common exposure effect across all components used in the failure composite endpoint. We included elective ICU admission in the model as we considered this factor to be clinically important with regards to postoperative bed utilization. The calibration and discrimination of the model was assessed using the Hosmer-Lemeshow goodness-of-fit test and estimating the area under the receiver characteristic operating curve (AUROC). Internal validation of the model was performed by bootstrapping 1000 samples and estimating the AUROC and 95% CI.

Statistical analyses were performed using STATA (version 13.1) software (STATA Corp, College Station, TX).

Using PASS (version 11) software (NCSS, Kaysville, UT), a sample size of 190 (19 failure and 171 success) patients will achieve 80% power to detect a difference of 0.20 between the AUROC under the null hypothesis of 0.70 (fair discrimination) and an AUROC under the alternative hypothesis of 0.50 (no discrimination) using a 2-sided z-test at a significance level of 0.05.

RESULTS

Of the 217 consecutive patients undergoing HBP surgery, 23 were not eligible (10 not available in the ward at time of recruitment, 5 refusals, 4 already participated in the study, 3 unable to consent and 1 had renal impairment). There were 25 failures of enhanced recovery (12.9%, 95% CI, 8.5% to 18.4%) in 194 patients undergoing major HBP surgery. Of the 94 elective ICU patients, 10 (10.6%) stayed in ICU for more than 24 hours after surgery. One patient was admitted to ICU unexpectedly due to surgical emphysema and stayed in ICU for 43 hours after surgery. There were 2 (2.1%) readmissions to ICU within 24 hours (1 for acute renal failure/atrial fibrillation and 1 for atelectasis), 2 reoperations (1.0%) and 11 hospital readmissions (11.6%). No patient died within 30 days after surgery.

The median postoperative length of hospital stay was longer in the failure group (13 days, 7 to 18) than in the successful group (7 days, 6 to 9) (P=0.003). This was mainly due to longer median length of postoperative hospital stay in patients undergoing hepatic surgery failing enhanced recovery management (12 days, 7 to

17) compared to those successfully managed (7 days, 6 to 9) (P=0.001). There were 26 patients undergoing pancreatic surgery. The median duration of postoperative hospital stay in patients undergoing pancreatic surgery failing and succeeding enhanced recovery management were 16 (5 to 35) and 10 (8 to 18) days, respectively (P=0.716). The median time from initial hospital discharge to readmission was 6 days (2 to 13).

The demographic and preoperative characteristics associated with failure of enhanced recovery protocol are shown in Table 1. Of the 137 patients with preoperative indocyanine green test results, 14 (7.2%) were classified as borderline and 4 (2.1%) were poor. There was no significant association between indocyanine green test results and failure groups (P=0.735).

Table 1. Demographic and preoperative factors associated with failure of enhanced recovery protocol after major hepatobiliary and pancreatic surgery

	Enhanced Recovery Protocol Groups		
	Failure (n=25)	Success (n=169)	P value
Mean age (SD), y	57 (11)	59 (11)	0.498
Males, n (%)	19 (76)	131 (78)	0.866
American Society of Anesthesiologists' Physical Status, n (%)			
I	2 (8)	25 (15)	
II	18 (72)	121 (72)	0.512
III/IV	5 (20)	23 (14)	
Current smoker, n (%)	9 (36)	35 (21)	0.088
Median adjusted cotinine, ng/mL (IQR)	1.34 (0.60 – 265.82)	1.07 (0.55 – 3.51)	0.183
Type of Surgery, n (%)			
Exploratory	1 (4)	5 (3)	
Laparoscopic liver resection	3 (12)	28 (17)	
Minor open liver resection	5 (20)	62 (37)	0.441
Major open liver ± biliary reconstruction	12 (48)	52 (31)	
Whipple	2 (8)	15 (9)	
Other pancreatic surgery	2 (8)	7 (4)	
Magnitude of Surgery, n (%)			
Major	4 (16)	36 (21)	0.541
Ultramajor	21 (84)	133 (79)	
Low albumin (<35 g/L), n (%)	2 (4)	12 (7)	0.698
High bilirubin (μmol/L)*, n(%)	7 (28)	27 (16)	0.159

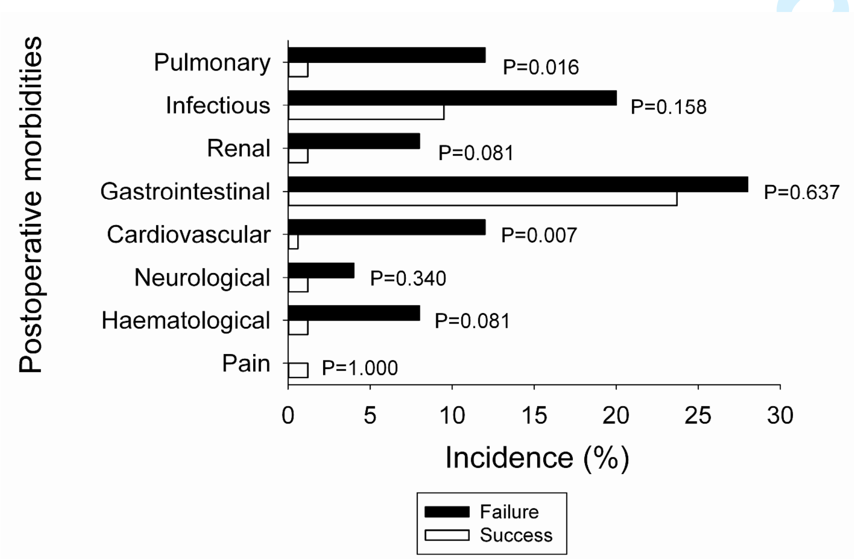
Alkaline Phosphatase (IU/L), n (%)			
Normal[†]	14 (56)	123 (73)	
Low	1 (4)	3 (2)	0.214
High	10 (40)	43 (25)	
High ALT/GPT(IU/L)[‡], n (%)	11 (44)	23 (14)	0.001
Haemoglobin (g/dL), n (%)			
Normal[§]	14 (56)	121 (72)	
Low	10 (40)	46 (27)	0.211
High	1 (4)	2 (1)	
Platelets, n (%)			
Normal (150-384 x 10^9/L)	14 (56)	117 (69)	
Low	10 (40)	50 (30)	0.294
High	1 (4)	2 (1)	
Prothrombin time, n (%)			
Normal (9.5-12 s)	19 (76)	144 (85)	
Low	0 (0)	1 (1)	0.423
High	6 (24)	24 (14)	
Activated partial thromboplastin time, n (%)			
Normal (28.2-37.4 s)	22 (88)	153 (91)	
Low	2 (8)	10 (6)	0.914
High	1 (4)	6 (4)	
High International Normalised Ratio, n (%)	0 (0)	2 (1)	1.000
Urinary Creatinine (μmol/L), n (%)			
Normal[†]	20 (80)	143 (85)	
Low	3 (12)	17 (10)	0.815
High	2 (8)	9 (5)	

*High bilirubin defined as more than 19μmol/L in males, and more than 17μmol/l in females
[†]Age and gender specific range
[‡]High Alanine transaminase/glutamic-pyruvic transaminase defined as more than 67 IU/L in males and more than 55 IU/L in females
[§]Normal range is 13.2 to 17.2g/dL for males and 11.9 to 15.1g/dL for females

The median duration of hepatic surgery was similar between failure (270 min, 186 to 336) and successful enhanced recovery groups (236 min, 180 to 315) (P=0.348). There was no difference in the median duration of pancreatic surgery between failure (395 min, 192 to 641) and successful enhanced recovery groups (488 min, 291 to 560) (P=0.933). The median Surgical Apgar Score was similar between failure (8, 6 to 9) and successful (8, 7 to 9) enhanced recovery groups (P=0.912).

Elective ICU admissions occurred in 13 (41.9%) patients undergoing laparoscopic liver resection, 19 (23.9%) minor open liver resection, 45 (70.3%) major open liver and/or biliary reconstruction, 15 (88.2%) Whipple and 2 (22.2%) other pancreatic surgery. Of the 94 elective ICU admissions, 17 (18.1%) patients failed enhanced recovery protocols after HBP surgery. Patients with elective ICU admissions were more likely to be enhanced recovery failures than patients sent to the ward after surgery ($RR_{unadjusted}$ 1.49, 95% CI, 1.09 to 2.05). The median duration of ICU length of stay was longer in the failure group (25 hours, 20 to 39) than in the successful enhanced recovery group (19 hours, 17 to 22) (P<0.001). However, the mean APACHE II score was similar between failure (13.6±3.8) and successful (12.3±3.5) enhanced recovery groups (P=0.150).

The overall incidence of postoperative morbidities was 35.1% (95% CI, 28.4% to 42.2%). There was no reported wound dehiscence (requiring surgical exploration or drainage of pus from the operation wound with or without isolation of organisms)[16] on the third postoperative day. There was no difference in the incidence of postoperative morbidities between groups according to the *a priori* Bonferroni-correction P value criterion (Figure 1). Patients with a postoperative morbidity were twice as likely to be a failure ($RR_{unadjusted}$ 2.36, 95% CI, 1.13 to 4.91) than those without. There was no difference in the mean EQ-5D index between failure (0.53 ± 0.30) and successful enhanced recovery groups (0.63 ± 0.29) (P=0.166).



After adjusting for planned postoperative ICU care, current smoking, high preoperative alanine transaminase/glutamic-pyruvic transaminase concentration and postoperative morbidities on the third day after surgery were significant risk factors associated with failure of enhanced recovery protocol (Table 2). The GEE model had adequate calibration (Hosmer-Lemeshow goodness-of-fit χ^2 8df, P=0.352) and excellent discrimination (AUROC = 0.87, 95% CI, 0.83 to 0.92).

Table 2. Risk factors for failure in enhanced recovery protocol after major hepatobiliary and pancreatic surgery using the generalized estimating equation model

	Common-effect RR (95% CI)	P value
ICU admission		
None	1.00	
Elective	0.41 (0.14 – 1.20)	0.104
Smoking status		
Never-smoker/Exsmoker	1.00	
Current smoker	2.21 (1.10 – 4.46)	0.027
ALT/GPT(IU/L)*		
Normal	1.00	
High	3.55 (1.68 – 7.49)	0.001
Any postoperative morbidity		
None	1.00	
Present on Day 3	2.69 (1.30 – 5.56)	0.007

*High Alanine transaminase/glutamic-pyruvic transaminase defined as more than 67 IU/L in males and more than 55 IU/L in females

DISCUSSION

Our management of patients undergoing HBP surgery incorporated a small proportion of evidence-based components described in ERAS programs for hepatic[4] and pancreatic[20] surgery. For every eight patients undergoing major HBP surgery, one was at risk of failing enhanced recovery protocols in major HBP surgery. However, no patients died within 30 days after surgery. Prolonged stay in ICU (12%) and hospital readmissions (6%) were the most common failure events.

Our hospital readmission rate and 30-day mortality are within the range described in studies included in recent systematic reviews of fast-track liver resection and pancreatic surgery.[1,2,20,21] Our patients who failed enhanced recovery protocols after major HBP surgery had clinically significantly longer ICU stays and postoperative stays in hospital.

Under half (48.5%) of our patients had elective ICU admission after surgery. Patients with elective ICU admissions after surgery were high-risk patients as suggested by the results of the univariate analysis where they were 1.5 times more likely to be failures than patients sent to the ward after surgery. However, when the elective ICU admission variable was included in the GEE model, the common-effect relative risk, although not significant (P=0.104), suggested a possible protective effect on failure. A previous study showed that intensive care physician staffing was associated with better outcomes after hepatic resection from prompt diagnosis and treatment of nonsurgical complications.[7] Our incidence of ICU readmission (2.1%) within 24 h appears acceptable. Previous studies included in systematic reviews of fast-track HBP surgery[1,2,20,21] have not reported the rate of ICU readmissions.

There is a paucity of studies examining the effect of smoking on fast-track surgery. Compared to conventional care programs, smoking was associated with 30-day hospital readmissions (odds ratio 1.60, 95% CI, 1.05 to 2.44), but not with prolonged length of hospital stay of more than 4 days (odds ratio 1.34, 95% CI, 0.92 to 1.95) in patients undergoing fast-track hip and knee arthroplasty.[22] However, current smoking was based on self-reported smoking history up to a month before hospital[22] and the effect of smoking on enhanced recovery failure is likely to be underestimated as many smokers (17%) deny smoking before elective surgery.[23] In contrast, we used both self-reported smoking history and adjusted urinary cotinine concentration to increase the accuracy of preoperative smoking status data. We have shown that current smokers were up to four times more likely to be enhanced recovery failures compared to never-smokers and former smokers in the GEE model. Thus, smoking cessation before HBP surgery would be expected to decrease the risk of enhanced recovery failures substantially. Smoking cessation at least 4 weeks, and preferably 8 weeks, before surgery significantly reduced the risk of postoperative respiratory and wound-healing complications.[24] Smoking is a modifiable risk factor that surgeons and anaesthesiologists can work on when patients are booked for surgery.

Of all the preoperative liver function and coagulation tests performed, high alanine transaminase/glutamic-pyruvic transaminases (ALT/GPT) concentration was the only independent biochemical risk factor associated with enhanced recovery failures. The strong association is indicative of the high risk of operating on an acutely inflamed liver.[25] A previous study[26] found that alanine aminotransferase ≥70 IU/L was an independent risk factor (odd ratio 2.02, 95% CI, 1.33 to 3.07) for postoperative complications after hepatic resection for hepatocellular carcinoma.

Fast-track open liver resection was associated with a reduction in general complications as defined by the Postoperative Morbidity Survey[16] by 36% (95% CI 16% to 52%).[18] A direct comparison between our incidence of postoperative morbidities on the third day after surgery and Jones et al.'s study[18] is difficult as the timing of their postoperative morbidities was not specified. Our GEE model found that patients with any postoperative morbidity on the third day after surgery were three times more likely to be an enhanced recovery failure than patients without reported postoperative morbidity. Specifically, after adjustment for multiple testing, cardiovascular events (diagnostic tests or treatment in last 24 h for new myocardial infarction or ischaemia, hypotension, arrhythmias, cardiogenic pulmonary oedema or thrombotic events)[16] was weakly associated with the risk of failure.

Using a minimal important difference of 0.03,[27] we found that patients in the enhanced recovery failure group had lower health-related quality of life than in the successful group. Our health-related quality of life on the third day after surgery in the successful group was similar to those reported in the standard care group by Jones et al.[18] Our practice does not include carbohydrate drink up to 2 hours before surgery, pharmacological prophylaxis for deep vein thrombosis or the routine use of epidural anaesthesia.

Overall, the results of this study suggest that it is possible to identify a subgroup of patients requiring additional care to minimize perioperative morbidity and length of stay. Patients who are smokers, have high ALT/GPT concentration or are at a high risk of postoperative morbidities are likely to fail enhanced recovery protocol in HBP surgery. In defining who is at high risk of postoperative morbidities, the American Society of Anesthesiologists' Physical Status grades III and IV and risk more than 50% estimated in the POSSUM-defined postoperative morbidity model may be useful as surrogate markers.[16] For those patients at high risk of HBP surgery failure, elective postoperative ICU admission and measures targeted to avoid postoperative cardiorespiratory complications are warranted to reduce the risk of failure of enhanced recovery events.

There are several limitations of this study. First, we did not measure the compliance rate of individual components of the ERAHBPS program. Recent studies suggest that 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.[28,29] Second, the common-effects GEE analysis was influenced by the higher frequencies of prolonged ICU length of stay (12%) and hospital readmissions (6%) events than other components included in the definition of failure. Our sample size was small for the use an average relative-effect GEE analysis[19] to address this problem. There is a potential for residual confounding despite the use of multivariate analyses in this cohort study. The applicability of the identified risk factors to select patients suitable for ERAHBPS programs in other settings requires further validation. Finally, the failure outcomes were limited to the early to intermediate phases of recovery; we did not measure late recovery outcomes, such as functional status and health-related quality of life beyond one month as recommended recently by Neville et al.[30]

In conclusion, patients who smoked, had elevated preoperative ALT/GPT or experienced postoperative morbidities were at risk of failing enhanced recovery protocols in major HBP surgery and may benefit from additional care. Patients who failed enhanced recovery protocols in HBP surgery stayed in ICU and in the hospital longer.

Acknowledgements

Funding Support: The work was substantially supported by the Health and Health Services Research Fund, Food and Health Bureau, Hong Kong SAR Government (Grant number: 08090311). The funding source had no role in the design, conduct or analysis of the study, or in the decision to submit the manuscript for publication.

Competing Interests: None declared.

Ethics approval: The Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee approved this cohort study of patients undergoing major HBP surgery at the Prince of Wales Hospital in Hong Kong between January 2011 and November 2012 (CRE-2013.181).

Contributors: AL performed the statistical analyses and had full access to all the data in the study. AL drafted the manuscript and made substantial revisions. All authors were involved in the study concept and design of the study. CHC collected the data. AL, MWAC, CDC, KFL, YSC and BSPL interpreted the data. All authors made critical revisions of the manuscript for important intellectual content and approved the final version of the manuscript. AL is guarantor.

Data sharing: No additional data available

Provenance and peer review: Not commissioned, externally peer reviewed.

REFERENCES

1. Spelt L, Ansari D, Sturesson C, et al. Fast-track programmes for hepatopancreatic resections: where do we stand? HPB (Oxford) 2011;13:833-8.
2. Hall TC, Dennison AR, Bilku DK, et al. Enhanced recovery programmes in hepatobiliary and pancreatic surgery: a systematic review. Ann R Coll Surg Engl 2012;94:318-26.
3. Lin DX, Li X, Ye QW, et al. Implementation of a fast-track clinical pathway decreases postoperative length of stay and hospital charges for liver resection. Cell Biochem Biophys 2011;61:413-9.
4. Wong-Lun-Hing EM, van Dam RM, Heijnen LA, et al. Is Current Perioperative Practice in Hepatic Surgery Based on Enhanced Recovery After Surgery (ERAS) Principles? World J Surg 2013.
5. Schultz NA, Larsen PN, Klarskov B, et al. Evaluation of a fast-track programme for patients undergoing liver resection. Br J Surg 2013;100:138-43.
6. Sanchez-Perez B, Aranda-Narvaez JM, Suarez-Munoz MA, et al. Fast-track program in laparoscopic liver surgery: Theory or fact? World J Gastrointest Surg 2012;4:246-50.
7. Dimick JB, Pronovost PJ, Lipsett PA. The Effect of ICU Physician Staffing and Hospital Volume on Outcomes After Hepatic Resection. J Intens Care Med 2002;17:41-7.

8. Constantinides VA, Tekkis PP, Fazil A, et al. Fast-track failure after cardiac surgery: development of a prediction model. Crit Care Med 2006;34:2875-82.

9. Lee A, Zhu F, Underwood MJ, Gomersall CD. Fast-track failure after cardiac surgery: external model validation and implications to ICU bed utilization. Crit Care Med 2013;41:1205-13.

10. Lee A, Chui PT, Chiu CH, et al. Risk of perioperative respiratory complications and postoperative morbidity in a cohort of adults exposed to passive smoking. Ann Surg 2014; Published Online First 6 February 2014. doi: 10.1097/SLA.0000000000000544

11. Lee KF, Cheung YS, Chong CN, et al. Laparoscopic versus open hepatectomy for liver tumours: a case control study. Hong Kong Med J 2007;13:442-8.

12. Lee KF, Cheung YS, Wong J, et al. Randomized clinical trial of open hepatectomy with or without intermittent Pringle manoeuvre. Br J Surg 2012;99:1203-9.

13. Maessen JM, Dejong CH, Kessels AG, von Meyenfeldt MF. Length of stay: an inappropriate readout of the success of enhanced recovery programs. World J Surg 2008;32:971-5.

14. Reynolds PQ, Sanders NW, Schildcrout JS, et al. Expansion of the surgical Apgar score across all surgical subspecialties as a means to predict postoperative mortality. Anesthesiology 2011;114:1305-12.

15. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.

16. Grocott MP, Browne JP, Van der Meulen J, et al. The Postoperative Morbidity Survey was validated and used to describe morbidity after major surgery. J Clin Epidemiol 2007;60:919-28.

17. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care 2005;43:203-20.

18. Jones C, Kelliher L, Dickinson M, et al. Randomized clinical trial on enhanced recovery versus standard care following open liver resection. Br J Surg 2013;100:1015-24.

19. Mascha EJ, Sessler DI. Statistical grand rounds: design and analysis of studies with binary- event composite endpoints: guidelines for anesthesia research. Anesth Analg 2011;112:1461-71.

20. Coolsen MM, van Dam RM, van der Wilt AA, et al. Systematic review and meta-analysis of enhanced recovery after pancreatic surgery with particular emphasis on pancreaticoduodenectomies. World J Surg 2013;37:1909-18.

21. Coolsen MM, Wong-Lun-Hing EM, van Dam RM, et al. A systematic review of outcomes in patients undergoing liver surgery in an enhanced recovery after surgery pathways. HPB (Oxford) 2013;15:245-51.

22. Jorgensen CC, Kehlet H. Outcomes in smokers and alcohol users after fast-track hip and knee arthroplasty. Acta Anaesthesiol Scand 2013;57:631-8.

23. Lee A, Gin T, Chui PT, et al. The accuracy of urinary cotinine immunoassay test strip as an add-on test to self-reported smoking before major elective surgery. Nicotine Tob Res 2013;15:1690-5.

24. Wong J, Lam DP, Abrishami A, et al. Short-term preoperative smoking cessation and postoperative complications: a systematic review and meta-analysis. Can J Anaesth 2012;59:268-79.

25. Schroeder RA, Marroquin CE, Bute BP, et al. Predictive indices of morbidity and mortality after liver resection. Ann Surg 2006;243:373-9.

26. Taketomi A, Kitagawa D, Itoh S, et al. Trends in morbidity and mortality after hepatic resection for hepatocellular carcinoma: an institute's experience with 625 patients. J Am Coll Surg 2007;204:580-7.

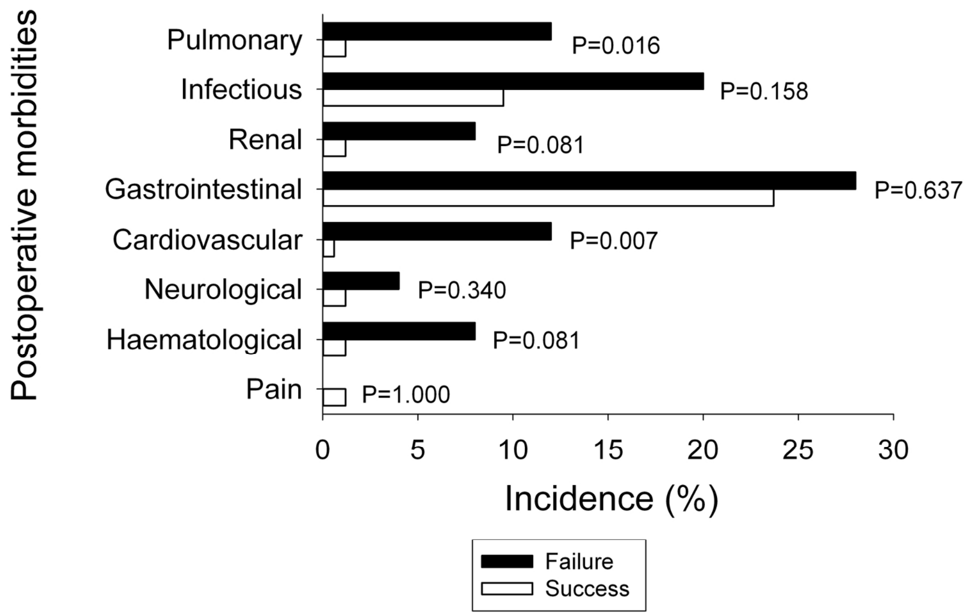
27. Barton GR, Sach TH, Doherty M, et al. An assessment of the discriminative ability of the EQ-5Dindex, SF-6D, and EQ VAS, using sociodemographic factors and clinical conditions. Eur J Health Econ 2008;9:237-49.

28. Gianotti L, Beretta S, Luperto M, et al. Enhanced recovery strategies in colorectal surgery: is the compliance with the whole program required to achieve the target? Int J Colorectal Dis 2014;29:329-41.

29. Nicholson A, Lowe MC, Parker J, et al. Systematic review and meta-analysis of enhanced recovery programmes in surgical patients. Br J Surg 2014;101:172-88.

30. Neville A, Lee L, Antonescu I, et al. Systematic review of outcomes used to evaluate enhanced recovery after surgery. Br J Surg 2014;101:159-71.

Figure 1. The incidence of postoperative morbidities on the third day after surgery by enhanced recovery protocol groups. To control for type I error at 0.05 from multiple comparisons, $P < 0.0063$ was considered significant



The incidence of postoperative morbidities on the third day after surgery by enhanced recovery protocol groups. To control for type I error at 0.05 from multiple comparisons, P < 0.0063 was considered significant.
86x56mm (600 x 600 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8, Tables 1 & 2 footnotes
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	No missing data
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	Not done
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	Text adequate
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	No missing data

		(c) Summarise follow-up time (eg, average and total amount)	9,10
Outcome data	15*	Report numbers of outcome events or summary measures over time	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2, 12-13
		(*b*) Report category boundaries when continuous variables were categorized	Tables footnotes
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14,17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Factors associated with failure of enhanced recovery protocol in patients undergoing major hepatobiliary and pancreatic surgery: a retrospective cohort study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005330.R1
Article Type:	Research
Date Submitted by the Author:	04-Jun-2014
Complete List of Authors:	Lee, Anna; The Chinese University of Hong Kong, Anaesthesia and Intensive Care Chiu, Chun Hung; The Chinese University of Hong Kong, Anaesthesia and Intensive Care Cho, Mui Wai Amy; The Chinese University of Hong Kong, Anaesthesia and Intensive Care Gomersall, Charles; The Chinese University of Hong Kong, Anaesthesia and Intensive Care Lee, Kit Fai; The Chinese University of Hong Kong, Division of Hepatobiliary and Pancreatic Surgery Cheung, Yue Sun; The Chinese University of Hong Kong, Division of Hepatobiliary and Pancreatic Surgery Lai, Paul Bo San; The Chinese University of Hong Kong, Division of Hepatobiliary and Pancreatic Surgery
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Health services research, Surgery
Keywords:	Hepatobiliary surgery < SURGERY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Factors associated with failure of enhanced recovery protocol in patients undergoing major hepatobiliary and pancreatic surgery: a retrospective cohort study

Anna LEE[1] , Chun Hung CHIU[1] , Mui Wai Amy CHO[1] , Charles David GOMERSALL[1] , Kit Fai LEE[2] , Yue Sun CHEUNG[2] , Paul Bo San LAI[2]

[1] Department of Anaesthesia and Intensive Care, Prince of Wales Hospital, The Chinese University of Hong Kong

[2] Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Prince of Wales Hospital, The Chinese University of Hong Kong

Address for correspondence: Anna Lee, Department of Anaesthesia and Intensive Care, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong

Phone: +852 2632 2735 Fax: +852 2637 2422 Email: annalee@cuhk.edu.hk

Reprints: Reprints will not be available from the authors

Category: Research article

Meeting: Presented in part at the combined Royal Australasian College of Surgeons Annual Scientific Congress and the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine Annual Scientific Meeting, in Singapore, 5th-9th May 2014.

MESH terms: Enhanced recovery after surgery; Postoperative care; Liver surgery; Pancreatic surgery; Cohort

Word count: 251 (Abstract); 4083 (Main text, including tables and figures)

ABSTRACT

Objective: This study examined the risk factors associated with failure of enhanced recovery protocol after major hepatobiliary and pancreatic (HBP) surgery.

Setting and participants: A retrospective cohort of 194 adults patients undergoing major HBP surgery at a university hospital in Hong Kong was followed up for 30 days. The patients were from a larger cohort study of 736 consecutive adults with preoperative urinary cotinine concentration to examine the association between passive smoking and risk of perioperative respiratory complications and postoperative morbidities.

Outcome measures: The primary outcome was failure of enhanced recovery protocol. This was defined as a composite measure of the following events: intensive care unit (ICU) stay more than 24 hours after surgery, unplanned admission to ICU within 30 days after surgery, hospital readmission, reoperation and mortality.

Results: There were 25 failures of enhanced recovery after HBP surgery (12.9%, 95% CI, 8.5% to 18.4%). After adjusting for elective ICU admission, smokers (RR 2.21, 95% CI, 1.10 to 4.46), high preoperative alanine transaminase/glutamic-pyruvic transaminase (RR 3.55, 1.68 to 7.49) and postoperative morbidities (RR 2.69, 95% CI, 1.30 to 5.56) were associated with failures of enhanced recovery in the generalized estimating equation risk model. Compared to those managed successfully, failures stayed longer in ICU (median 19 *vs.* 25 hours, $P<0.001$) and in hospital for postoperative care (median 7 *vs.* 13 days, $P=0.003$).

Conclusion: Smokers and patients having high preoperative alanine transaminase/glutamic-pyruvic transaminase concentration or have a high risk of postoperative morbidities are likely to fail enhanced recovery protocol in HBP surgery programs.

Strengths and limitations of this study

- This is the first study to identify risk factors associated with the failure of enhanced recovery protocol in major hepatobiliary and pancreatic surgery.
- Instead of using length of hospital stay as an endpoint, failure was defined as a composite measure of slow recovery: length of stay in the intensive care unit (ICU) more than 24 hours after surgery, unplanned admission to ICU within 30 days, readmission to the hospital within 30 days after surgery, reoperation for complications and 30-day mortality
- Smokers (defined by self-reported history and adjusted urinary cotinine concentration) and patients having high preoperative alanine transaminase glutamic-pyruvic transaminase concentration or have a high risk of postoperative morbidities are likely to fail clinical pathways in fast-track hepatobiliary and pancreatic surgery. Similar results were found in a sensitivity analysis using adjusted urinary cotinine concentrations.
- We did not consider the compliance rate of individual components of the early recovery after hepatobiliary pancreatic surgery program
- High risk patients at risk of failing enhanced recovery protocols in major hepatobiliary pancreatic surgery may benefit from additional care to minimize perioperative morbidities and length of stay.

INTRODUCTION

Enhanced recovery after major hepatobiliary and pancreatic surgery (ERAHBPS) is a complex intervention that includes many of the following components: patient and family education, no bowel preparation, no preanaesthetic medication, preoperative carbohydrate loading, thromboembolic prophylaxis, antiemetic prophylaxis, epidural analgesia, intraoperative normothermia, prophylactic antibiotics, no systemic opioids, fluid restriction, no surgical drains, no standard postoperative nasogastric tubes, postoperative nutritional care and early mobilization.[1]

Recent systematic reviews[1;2] of several observational studies of ERAHBPS programs suggest that it is safe and feasible. Compared to traditional clinical pathways, fast-track hepatobiliary and pancreatic (HBP) surgery programs have similar risks of readmission, morbidity and mortality[1-3] and reduced the duration of postoperative length of stay and overall hospital cost.[3] However, compliance with core components of enhance recovery after liver surgery program vary between high-volume European centers, with a median adoption of 9 (range 7 to 12) of 22 core elements.[4]

As with all enhanced recovery after surgery (ERAS) programs, a small proportion of patients will fail fast-track HBP surgery and require additional intensive care unit (ICU) resources. Although not all fast-track HBP surgical patients are routinely admitted to ICU after their procedure,[5;6] ICU care after liver resection was associated with a decreased risk in hospital mortality (odds ratio 0.26, 95% CI 0.10 to 0.71) and a reduction in total hospital costs (13%).[7] These results suggest that careful selection of patients for ERAHBPS is crucial for maximizing the efficiency of perioperative care pathways.

Fast-track failure risk models after cardiac surgery have been developed[8] and externally validated[9] to facilitate the planning of perioperative care pathways, but factors associated with failure of enhanced recovery protocol after HBP surgery are unknown. The objectives of this study were to estimate the incidence of and identify the risk factors associated with failure of enhanced recovery protocol after HBP surgery. And with such information, we can identify a subgroup of patients at risk of failure to provide additional care to minimize perioperative morbidities and length of stay.

METHODS

Study cohort

The Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee approved this retrospective cohort study of patients undergoing major HBP surgery at the Prince of Wales Hospital in Hong Kong between January 2011 and November 2012 (CRE-2013.181). The patients were from a larger cohort study of 736 consecutive adult patients with preoperative urinary cotinine concentration to examine the association between passive smoking and risk of perioperative respiratory complications and postoperative morbidities.[10] All patients gave written informed consent before surgery. Patients undergoing other types of surgery, unable to give written informed consent, having chronic renal failure, younger than 18 years and urine cotinine samples collected more than 48 h before surgery were excluded.

The types of surgery included were laparoscopic liver resection (nonanatomical wedge resections, or resection of 1 or 2 segments), minor open liver resection (fewer than 3 segments including multiple non-anatomical resections), major open liver resections (3 or more segments), liver resection with biliary reconstruction[11;12] and pancreatic surgery. Pancreatic surgery included Whipple's procedure, double bypass (hepaticojejunostomy and gastrojejunostomy in unresectable cancer of the head of pancreas) and distal pancreatectomy.

Typical management

The typical clinical care pathway for HBP surgical patients involved the following: admission to surgical ward one day before surgery, patient education, no preanaesthetic medication, mechanical prophylaxis for deep vein thrombosis, intraoperative prophylactic antibiotics, normothermia during surgery, ICU or surgical ward for first 24 h after surgery, surgical ward, early mobilization and hospital discharge (Table 1). The use of epidural anaesthesia/analgesia is not routine because of concerns about postoperative coagulopathy in patients with cirrhosis of liver.[13] Patients were given patient controlled morphine analgesia.

Although there was no formalized extubation protocol, extubation at the end of liver resection surgery or within 1 h after admission to ICU was expected; for pancreatic surgery where most patients went to ICU, extubation within 4 h was expected. There is no surgical high dependency unit at the Prince of Wales Hospital, Hong Kong.

Drains were removed as soon as possible when there was no biliary or pancreatic anastomiotic leakage. In patients undergoing liver surgery, gradual resumption of diet from liquid to solid food was expected during the first three days after surgery. For Whipple's operation, the diet resumption was slower, starting from the fifth postoperative day and a normal diet was expected by the seventh. For patients who could not tolerate oral intake by the seventh day after surgery, parenteral nutrition was given with a target of 25-30kcal/kg.

Table 1. Enhanced recovery elements in liver and pancreatic resectional surgery

	Liver resection	**Pancreatic resection**
Pre-operatively	Information given to patient and patient education No premedication	Information given to patient and patient education No premedication
Day 0	Normothermia during surgery Mechanical prophylaxis for deep vein thrombosis Intraoperative prophylactic antibiotics No nasogastric tube No routine abdominal drain	Normothermia during surgery Mechanical prophylaxis for deep vein thrombosis Intraoperative prophylactic antibiotics Routine nasogastric and abdominal drain only for Whipple's operation
Day 1	Patient controlled morphine analgesia Oral fluid Moving patient to chair	Patient controlled morphine analgesia Oral fluid Moving patient to chair
Day 2	Fluid diet Enhanced mobilization Removal of urinary catheter	Enhanced mobilization
Day 3	Soft diet Removal of drain	Removal of urinary catheter Removal of nasogastric tube if draining <300ml
Day 4	Normal diet	Fluid diet Removal of drain
Day 5	Discharge if no fever, pain can be controlled with oral analgesics and patient has adequate mobilization	Soft diet
Day 6		Normal diet
Day 7		Discharge if no fever, pain can be controlled with oral analgesics and patient has adequate mobilization

Outcome Measure

For the purposes of this study, we define failure of enhanced recovery protocol after HBP surgery as a composite measure of the following events: length of ICU stay more than 24 h after surgery, unplanned admission to ICU within 30 days after surgery, readmission to the hospital within 30 days after surgery, reoperation for complications and 30-day mortality. These events were chosen as markers of slow recovery and are common quality of care indicators. Unlike previous ERAS studies, we did not chose length of stay as a primary outcome as it has been shown that reductions in length of stay up to a median of 2 days may be related to changes in organization of care and not to the effect of the ERAS program.[14]

We collected patient demographics, smoking status, preoperative urinary cotinine concentration that was adjusted for creatinine level, American Society of Anesthesiologists' Physical Status, Surgical Apgar score,[15] duration of surgery, ICU admission details, APACHE II (severity of illness score in patients admitted to ICU),[16] preoperative liver function tests, indocyanine green test and coagulation tests, and failure events from the hospital electronic Clinical Management System database. The research staff collected postoperative morbidities (pulmonary, infectious, renal, gastrointestinal, cardiovascular, neurological, haematological, wound and severe pain) on the third day after surgery using a reliable and valid Postoperative Morbidity Survey questionnaire.[17] The EQ-5D index, a health-related quality of life using a US set of reference weights, was measured on the third day after surgery[18] as the greatest difference in EQ-5D index between ERAHBPS and standard care occur between postoperative day 2 and 5.[19] 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] The research staff was blinded to the urinary cotinine concentration results.

Statistical Analysis

Continuous data were expressed as mean and standard deviation (SD) or median and interquartile range (IQR). The 95% confidence interval (95% CI) was estimated around the incidence of HBP surgery failure. Appropriate Student t-tests, Mann-Whitney U tests, χ^2 analyses or exact tests were used to compare factors associated with failure of enhanced recovery protocol. To adjust for multiple testing of individual postoperative morbidity events, a Bonferroni correction was used so that the significance criterion was set at $P<0.0063$. There was no missing data.

A generalized estimating equation (GEE) model with a Poisson distribution, log-link function and exchangeable correlation[20] was used to obtain a common-effect relative risk (RR) of failure of enhanced recovery protocol after HBP surgery. This GEE model was more appropriate for analysis of composite measures and assumes that there is a single common exposure effect across all components used in the failure composite endpoint. We included elective ICU admission in the model as we considered this factor to be clinically important with regards to postoperative bed utilization. The calibration and discrimination of the model was assessed using the Hosmer-Lemeshow goodness-of-fit test and estimating the area under the receiver characteristic operating curve (AUROC). Internal validation of the model was performed by bootstrapping 1000 samples and estimating the AUROC and 95% CI. A sensitivity analysis of the GEE model was performed by including adjusted urinary cotinine concentration as a continuous variable instead of smoking status as a categorical independent variable. Statistical analyses were performed using STATA (version 13.1) software (STATA Corp, College Station, TX).

Using PASS (version 11) software (NCSS, Kaysville, UT), a sample size of 190 (19 failure and 171 success) patients will achieve 80% power to detect a difference of 0.20 between the AUROC under the null hypothesis of 0.70 (fair discrimination) and an AUROC under the alternative hypothesis of 0.50 (no discrimination) using a 2-sided z-test at a significance level of 0.05.

RESULTS

Of the 217 consecutive patients undergoing HBP surgery, 23 were not eligible (10 not available in the ward at time of recruitment, 5 refusals, 4 already participated in the study, 3 unable to consent and 1 had renal impairment). There were 25 failures of enhanced recovery (12.9%, 95% CI, 8.5% to 18.4%) in 194 patients undergoing major HBP surgery. Of the 94 elective ICU patients, 10 (10.6%) stayed in ICU for more than 24 hours after surgery. One patient was admitted to ICU unexpectedly due to surgical emphysema and stayed in ICU for 43 hours after surgery. There were 2 (2.1%) readmissions to ICU within 24 hours (1 for acute renal failure/atrial fibrillation and 1 for atelectasis), 2 reoperations (1.0%) and 11 hospital readmissions (5.6%). The reasons for hospital readmissions were abdominal complications (n=5), wound complications (n=3), pyrexia with or without chills (n=2) and jaundice (n=1). No patient died within 30 days after surgery.

The median postoperative length of hospital stay was longer in the failure group (13 days, 7 to 18) than in the successful group (7 days, 6 to 9) (P=0.003). This was mainly due to longer median length of postoperative hospital stay in patients undergoing hepatic surgery failing enhanced recovery management (12 days, 7 to 17) compared to those successfully managed (7 days, 6 to 9) (P=0.001). There were 26 patients undergoing pancreatic surgery. The median duration of postoperative hospital stay in patients undergoing pancreatic surgery failing and succeeding enhanced recovery management were 16 (5 to 35) and 10 (8 to 18) days, respectively (P=0.716). The median time from initial hospital discharge to readmission was 6 days (2 to 13).

The demographic and preoperative characteristics associated with failure of enhanced recovery protocol are shown in Table 2. Of the 137 patients with preoperative indocyanine green test results, 14 (7.2%) were classified as borderline and 4 (2.1%) were poor. There was no significant association between indocyanine green test results and failure groups (P=0.735).

Table 2. Demographic and preoperative factors associated with failure of enhanced recovery protocol after major hepatobiliary and pancreatic surgery

	Enhanced Recovery Protocol Groups		
	Failure (n=25)	Success (n=169)	P value
Mean age (SD), y	57 (11)	59 (11)	0.498
Males, n (%)	19 (76)	131 (78)	0.866
American Society of Anesthesiologists' Physical Status, n (%)			
I	2 (8)	25 (15)	
II	18 (72)	121 (72)	0.512
III/IV	5 (20)	23 (14)	
Current smoker, n (%)	9 (36)	35 (21)	0.088
Median adjusted cotinine, ng/mL (IQR)	1.34 (0.60 – 265.82)	1.07 (0.55 – 3.51)	0.183
Type of Surgery, n (%)			
Exploratory	1 (4)	5 (3)	
Laparoscopic liver resection	3 (12)	28 (17)	
Minor open liver resection	5 (20)	62 (37)	0.441
Major open liver ± biliary reconstruction	12 (48)	52 (31)	
Whipple	2 (8)	15 (9)	
Other pancreatic surgery	2 (8)	7 (4)	
Magnitude of Surgery, n (%)			

Major	4 (16)	36 (21)	0.541
Ultramajor	21 (84)	133 (79)	
Low albumin (<35 g/L), n (%)	2 (4)	12 (7)	0.698
High bilirubin (μmol/L)*, n(%)	7 (28)	27 (16)	0.159
Alkaline Phosphatase (IU/L), n (%)			
Normal†	14 (56)	123 (73)	
Low	1 (4)	3 (2)	0.214
High	10 (40)	43 (25)	
High ALT/GPT(IU/L)‡, n (%)	11 (44)	23 (14)	0.001
Haemoglobin (g/dL), n (%)			
Normal§	14 (56)	121 (72)	
Low	10 (40)	46 (27)	0.211
High	1 (4)	2 (1)	
Platelets, n (%)			
Normal (150-384 x 10^9/L)	14 (56)	117 (69)	
Low	10 (40)	50 (30)	0.294
High	1 (4)	2 (1)	
Prothrombin time, n (%)			
Normal (9.5-12 s)	19 (76)	144 (85)	
Low	0 (0)	1 (1)	0.423
High	6 (24)	24 (14)	
Activated partial thromboplastin time, n (%)			
Normal (28.2-37.4 s)	22 (88)	153 (91)	
Low	2 (8)	10 (6)	0.914
High	1 (4)	6 (4)	
High International Normalised Ratio, n (%)	0 (0)	2 (1)	1.000
Urinary Creatinine (μmol/L), n (%)			
Normal†	20 (80)	143 (85)	
Low	3 (12)	17 (10)	0.815
High	2 (8)	9 (5)	

*High bilirubin defined as more than 19μmol/L in males, and more than 17μmol/l in females
†Age and gender specific range
‡High Alanine transaminase/glutamic-pyruvic transaminase defined as more than 67 IU/L in males and more than 55 IU/L in females
§Normal range is 13.2 to 17.2g/dL for males and 11.9 to 15.1g/dL for females

The median duration of hepatic surgery was similar between failure (270 min, 186 to 336) and successful enhanced recovery groups (236 min, 180 to 315) (P=0.348). There was no difference in the median duration of pancreatic surgery between failure (395 min, 192 to 641) and successful enhanced recovery groups (488 min, 291 to 560) (P=0.933). The median Surgical Apgar Score was similar between failure (8, 6 to 9) and successful (8, 7 to 9) enhanced recovery groups (P=0.912).

Elective ICU admissions occurred in 13 (41.9%) patients undergoing laparoscopic liver resection, 19 (23.9%) minor open liver resection, 45 (70.3%) major open liver and/or biliary reconstruction, 15 (88.2%) Whipple and 2 (22.2%) other pancreatic surgery. Of the 94 elective ICU admissions, 17 (18.1%) patients failed enhanced recovery protocols after HBP surgery. Patients with elective ICU admissions were more likely to be enhanced recovery failures than patients sent to the ward after surgery ($RR_{unadjusted}$ 1.49, 95% CI, 1.09 to 2.05). The median duration of ICU length of stay was longer in the failure group (25 hours, 20 to 39) than in the successful enhanced recovery group (19 hours, 17 to 22) (P<0.001). However, the mean APACHE II score was similar between failure (13.6±3.8) and successful (12.3±3.5) enhanced recovery groups (P=0.150).

The overall incidence of postoperative morbidities was 35.1% (95% CI, 28.4% to 42.2%). There was no reported wound dehiscence (requiring surgical exploration or drainage of pus from the operation wound with or without isolation of organisms)[17] on the third postoperative day. There was no difference in the incidence of postoperative morbidities between groups according to the *a priori* Bonferroni-correction P value criterion (Figure 1). Patients with a postoperative morbidity were twice as likely to be a failure ($RR_{unadjusted}$ 2.36, 95% CI, 1.13 to 4.91) than those without. There was no difference in the mean EQ-5D index between failure (0.53 ± 0.30) and successful enhanced recovery groups (0.63 ± 0.29) (P=0.166).

After adjusting for planned postoperative ICU care, current smoking, high preoperative alanine transaminase/glutamic-pyruvic transaminase concentration and postoperative morbidities on the third day after surgery were significant risk factors associated with failure of enhanced recovery protocol (Table 3). The GEE model had adequate calibration (Hosmer-Lemeshow goodness-of-fit χ^2 8df, P=0.352) and excellent discrimination (AUROC = 0.87, 95% CI, 0.83 to 0.92).

Table 3. Risk factors for failure in enhanced recovery protocol after major hepatobiliary and pancreatic surgery using the generalized estimating equation model

	Common-effect RR (95% CI)	**P value**
ICU admission		
None	1.00	
Elective	0.41 (0.14 – 1.20)	0.104
Smoking status		
Never-smoker/Exsmoker	1.00	
Current smoker	2.21 (1.10 – 4.46)	0.027
ALT/GPT(IU/L)*		
Normal	1.00	
High	3.55 (1.68 – 7.49)	0.001
Any postoperative morbidity		
None	1.00	
Present on Day 3	2.69 (1.30 – 5.56)	0.007

*High Alanine transaminase/glutamic-pyruvic transaminase defined as more than 67 IU/L in males and more than 55 IU/L in females

The results of a sensitivity analysis on the main GEE model using adjusted urinary cotinine concentration instead of smoking status are shown Table 4. Compared to patients with nil urinary cotinine concentration, the predicted adjusted risk for failure in enhanced recovery protocol in patients with urinary cotinine concentrations of 50, 500 and 1500 ng/ml were 1.04 (95% CI, 1.01 to 1.07), 1.52 (95% CI, 1.22 to 1.90) and 3.51 (95% CI, 1.80 to 6.83) respectively. The GEE model had adequate calibration (Hosmer-Lemeshow goodness-of-fit χ^2 8df, P=0.496) and excellent discrimination (AUROC = 0.87, 95% CI, 0.82 to 0.91).

Table 4. Sensitivity analysis on the risk factors for failure in enhanced recovery protocol after major hepatobiliary and pancreatic surgery

	Common-effect RR (95% CI)	**P value**
ICU admission		
None	1.000	
Elective	0.505 (0.176 – 1.444)	0.202
Adjusted cotinine concentration (ng/ml)*	1.001 (1.000 – 1.001)	<0.001
ALT/GPT(IU/L)†		
Normal	1.000	
High	4.626 (2.097 – 10.207)	<0.001
Any postoperative morbidity		
None	1.000	

Present on Day 3	2.657 (1.312 – 5.379)	0.007

*Active smokers commonly defined as urinary cotinine concentration >50ng/ml[21]
†High Alanine transaminase/glutamic-pyruvic transaminase defined as more than 67 IU/L in males and more than 55 IU/L in females

DISCUSSION

Our management of patients undergoing HBP surgery incorporated a small proportion of evidence-based components described in ERAS programs for hepatic[4] and pancreatic[22] surgery. For every eight patients undergoing major HBP surgery, one was at risk of failing enhanced recovery protocols in major HBP surgery. However, no patients died within 30 days after surgery. 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. Prolonged stay in ICU (12%) and hospital readmissions (6%) were the most common failure events. Our hospital readmission rate and 30-day mortality are within the range described in studies included in recent systematic reviews of fast-track liver resection and pancreatic surgery.[1;2;22;23] Our patients who failed enhanced recovery protocols after major HBP surgery had clinically significantly longer ICU stays and postoperative stays in hospital.

Access to ICU admission after surgery affects outcomes.[24] Under half (48.5%) of our patients had elective ICU admission after surgery. Patients with elective ICU admissions after surgery were high-risk patients as suggested by the results of the univariate analysis where they were 1.5 times more likely to be failures than patients sent to the ward after surgery. However, when the elective ICU admission variable was included in the GEE models, the common-effect relative risk, although not significant, suggested a possible protective effect on failure. A previous study showed that intensive care physician staffing was associated with better outcomes after hepatic resection from prompt diagnosis and treatment of nonsurgical complications.[7] Our incidence of ICU readmission (2.1%) within 24 h appears acceptable. Previous studies included in systematic reviews of fast-track HBP surgery[1;2;22;23] have not reported the rate of ICU readmissions.

There is a paucity of studies examining the effect of smoking on fast-track surgery. Compared to conventional care programs, smoking was associated with 30-day hospital readmissions (odds ratio 1.60, 95% CI, 1.05 to 2.44), but not with prolonged length of hospital stay of more than 4 days (odds ratio 1.34, 95% CI, 0.92 to 1.95) in patients undergoing fast-track hip and knee arthroplasty.[25] However, current smoking was based on self-reported smoking history up to a month before hospital[25] and the effect of smoking on enhanced recovery failure is likely to be underestimated as many smokers (17%) deny smoking before elective surgery.[26] In contrast, we used both self-reported smoking history and adjusted urinary cotinine concentration to increase the accuracy of preoperative smoking status data. We have shown that current smokers were up to four times more likely to be enhanced recovery failures compared to never-smokers and former smokers in the GEE model. The results of the sensitivity analysis using adjusted urinary cotinine concentration further strengthens the association between smoking and the risk of enhanced recovery failure. Thus, smoking cessation before HBP surgery would be expected to decrease the risk of enhanced recovery failures substantially. Smoking cessation at least 4 weeks, and preferably 8 weeks, before surgery significantly reduced the risk of postoperative respiratory and wound-healing complications.[27] Smoking is a modifiable risk factor that surgeons and anaesthesiologists can work on when patients are booked for surgery.

Of all the preoperative liver function and coagulation tests performed, high alanine transaminase/glutamic-pyruvic transaminases (ALT/GPT) concentration was the only independent biochemical risk factor associated with enhanced recovery failures. The strong association is indicative of the high risk of operating on an acutely inflamed liver.[28] A previous study[29] found that alanine aminotransferase ≥70 IU/L was an independent risk factor (odd ratio 2.02, 95% CI, 1.33 to 3.07) for postoperative complications after hepatic resection for hepatocellular carcinoma.

Fast-track open liver resection was associated with a reduction in general complications as defined by the Postoperative Morbidity Survey[17] by 36% (95% CI 16% to 52%).[19] A direct comparison between our incidence of postoperative morbidities on the third day after surgery and Jones et al.'s study[19] is difficult as the timing of their postoperative morbidities was not specified. Our GEE model found that patients with any postoperative morbidity on the third day after surgery were three times more likely to be an enhanced recovery failure than patients without reported postoperative morbidity. Specifically, after adjustment for multiple testing, cardiovascular events (diagnostic tests or treatment in last 24 h for new myocardial infarction or ischaemia, hypotension, arrhythmias, cardiogenic pulmonary oedema or thrombotic events)[17] was weakly associated with the risk of failure. Early postoperative morbidities are associated with longer duration of hospital stay[30] and an increased risk of hospital readmission.[31]

Using a minimal important difference of 0.03,[32] we found that patients in the enhanced recovery failure group had lower health-related quality of life than in the successful group. Our health-related quality of life on the third day after surgery in the successful group was similar to those reported in the standard care group by Jones et al.[19] Our practice does not include carbohydrate drink up to 2 hours before surgery, pharmacological prophylaxis for deep vein thrombosis or the routine use of epidural anaesthesia.

Overall, the results of this study suggest that it is possible to identify a subgroup of patients requiring additional care to minimize perioperative morbidity and length of stay. Patients who are smokers, have high ALT/GPT concentration or are at a high risk of postoperative morbidities are likely to fail enhanced recovery protocol in HBP surgery. In defining who is at high risk of postoperative morbidities, the American Society of Anesthesiologists' Physical Status grades III and IV and risk more than 50% estimated in the POSSUM-defined postoperative morbidity model may be useful as surrogate markers.[17] For those patients at high risk of HBP surgery failure, elective postoperative ICU admission and measures targeted to avoid postoperative cardiorespiratory complications are warranted to reduce the risk of failure of enhanced recovery events.

There are several limitations of this study. First, we did not measure the compliance rate of individual components of the ERAHBPS program. Recent studies suggest that 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] Second, the common-effects GEE analysis was influenced by the higher frequencies of prolonged ICU length of stay (12%) and hospital readmissions (6%) events than other components included in the definition of failure. Our sample size was small for the use an average relative-effect GEE analysis[20] to address this problem. There is a potential for residual confounding despite the use of multivariate analyses in this cohort study. The applicability of the identified risk factors to select patients suitable for ERAHBPS programs in other settings requires further validation. Finally, the failure outcomes were limited to the early to intermediate phases of recovery; we did not measure outpatient complications[31] or late recovery outcomes, such as functional status and health-related quality of life beyond one month as recommended recently by Neville et al.[35]

In conclusion, patients who smoked, had elevated preoperative ALT/GPT or experienced postoperative morbidities were at risk of failing enhanced recovery protocols in major HBP surgery and may benefit from additional care. Patients who failed enhanced recovery protocols in HBP surgery stayed in ICU and in the hospital longer.

Acknowledgements

Funding Support: The work was substantially supported by the Health and Health Services Research Fund, Food and Health Bureau, Hong Kong SAR Government (Grant number: 08090311). The funding source had no role in the design, conduct or analysis of the study, or in the decision to submit the manuscript for publication.

Competing Interests: None declared.

Ethics approval: The Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee approved this cohort study of patients undergoing major HBP surgery at the Prince of Wales Hospital in Hong Kong between January 2011 and November 2012 (CRE-2013.181).

Contributors: AL performed the statistical analyses and had full access to all the data in the study. AL drafted the manuscript and made substantial revisions. All authors were involved in the study concept and design of the study. CHC collected the data. AL, MWAC, CDC, KFL, YSC and BSPL interpreted the data. All authors made critical revisions of the manuscript for important intellectual content and approved the final version of the manuscript. AL is guarantor.

Data sharing: No additional data available

Provenance and peer review: Not commissioned, externally peer reviewed.

References

(1) Spelt L, Ansari D, Sturesson C, et al. Fast-track programmes for hepatopancreatic resections: where do we stand? *HPB (Oxford)* 2011; 13(12):833-838.

(2) Hall TC, Dennison AR, Bilku DK, et al. Enhanced recovery programmes in hepatobiliary and pancreatic surgery: a systematic review. *Ann R Coll Surg Engl* 2012; 94(5):318-326.

(3) Lin DX, Li X, Ye QW, et al. Implementation of a fast-track clinical pathway decreases postoperative length of stay and hospital charges for liver resection. *Cell Biochem Biophys* 2011; 61(2):413-419.

(4) Wong-Lun-Hing EM, van Dam RM, Heijnen LA, et al. Is Current Perioperative Practice in Hepatic Surgery Based on Enhanced Recovery After Surgery (ERAS) Principles? *World J Surg* 2013.

(5) Schultz NA, Larsen PN, Klarskov B, et al. Evaluation of a fast-track programme for patients undergoing liver resection. *Br J Surg* 2013; 100(1):138-143.

(6) Sanchez-Perez B, Aranda-Narvaez JM, Suarez-Munoz MA, et al. Fast-track program in laparoscopic liver surgery: Theory or fact? *World J Gastrointest Surg* 2012; 4(11):246-250.

(7) Dimick JB, Pronovost PJ, Lipsett PA. The Effect of ICU Physician Staffing and Hospital Volume on Outcomes After Hepatic Resection. *J Intens Care Med* 2002; 17:41-47.

(8) Constantinides VA, Tekkis PP, Fazil A, et al. Fast-track failure after cardiac surgery: development of a prediction model. *Crit Care Med* 2006; 34(12):2875-2882.

(9) Lee A, Zhu F, Underwood MJ, et al. Fast-track failure after cardiac surgery: external model validation and implications to ICU bed utilization. *Crit Care Med* 2013; 41(5):1205-1213.

(10) Lee A, Chui PT, Chiu CH, et al. Risk of perioperative respiratory complications and postoperative morbidity in a cohort of adults exposed to passive smoking. *Ann Surg* 2014; Feb 6 [epub ahead].

(11) Lee KF, Cheung YS, Chong CN, et al. Laparoscopic versus open hepatectomy for liver tumours: a case control study. *Hong Kong Med J* 2007; 13(6):442-448.

(12) Lee KF, Cheung YS, Wong J, et al. Randomized clinical trial of open hepatectomy with or without intermittent Pringle manoeuvre. *Br J Surg* 2012; 99(9):1203-1209.

(13) Shontz R, Karuparthy V, Temple R, et al.Prevalence and risk factors predisposing to coagulopathy in patients receiving epidural analgesia for hepatic surgery. *Reg Anesth Pain Med* 2009; 34(4):308-311.

(14) Maessen JM, Dejong CH, Kessels AG, et al. Length of stay: an inappropriate readout of the success of enhanced recovery programs. *World J Surg* 2008; 32(6):971-975.

(15) Reynolds PQ, Sanders NW, Schildcrout JS, et al. Expansion of the surgical Apgar score across all surgical subspecialties as a means to predict postoperative mortality. *Anesthesiology* 2011; 114(6):1305-1312.

(16) Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; 13(10):818-829.

(17) Grocott MP, Browne JP, Van der Meulen J, et al. The Postoperative Morbidity Survey was validated and used to describe morbidity after major surgery. *J Clin Epidemiol* 2007; 60(9):919-928.

(18) Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. *Med Care* 2005; 43(3):203-220.

(19) Jones C, Kelliher L, Dickinson M, et al. Randomized clinical trial on enhanced recovery versus standard care following open liver resection. *Br J Surg* 2013; 100(8):1015-1024.

(20) Mascha EJ, Sessler DI. Statistical grand rounds: design and analysis of studies with binary- event composite endpoints: guidelines for anesthesia research. *Anesth Analg* 2011; 112(6):1461-1471.

(21) SRNT Subcommittee on biochemical verification. Biochemical verification of tobacco use and cessation. *Nicotine Tob Res* 2002; 4(2):149-159.

(22) Coolsen MM, van Dam RM, van der Wilt AA, et al. Systematic review and meta-analysis of enhanced recovery after pancreatic surgery with particular emphasis on pancreaticoduodenectomies. *World J Surg* 2013; 37(8):1909-1918.

(23) Coolsen MM, Wong-Lun-Hing EM, van Dam RM, et al. A systematic review of outcomes in patients undergoing liver surgery in an enhanced recovery after surgery pathways. *HPB (Oxford)* 2013; 15(4):245-251.

(24) Pearse RM, Moreno RP, Bauer P, et al. Mortality after surgery in Europe: a 7 day cohort study. *Lancet* 2012; 380(9847):1059-1065.

(25) Jorgensen CC, Kehlet H. Outcomes in smokers and alcohol users after fast-track hip and knee arthroplasty. *Acta Anaesthesiol Scand* 2013; 57(5):631-638.

(26) Lee A, Gin T, Chui PT, et al. The accuracy of urinary cotinine immunoassay test strip as an add-on test to self-reported smoking before major elective surgery. *Nicotine Tob Res* 2013; 15(10):1690-1695.

(27) Wong J, Lam DP, Abrishami A, et al. Short-term preoperative smoking cessation and postoperative complications: a systematic review and meta-analysis. *Can J Anaesth* 2012; 59(3):268-279.

(28) Schroeder RA, Marroquin CE, Bute BP, et al.Predictive indices of morbidity and mortality after liver resection. *Ann Surg* 2006; 243(3):373-379.

(29) Taketomi A, Kitagawa D, Itoh S, et al. Trends in morbidity and mortality after hepatic resection for hepatocellular carcinoma: an institute's experience with 625 patients. *J Am Coll Surg* 2007; 204(4):580-587.

(30) Davies SJ, Francis J, Dilley J, et al. Measuring outcomes after major abdominal surgery during hospitalization: reliability and validity of the Postoperative Morbidity Survey. *Perioper Med (Lond)* 2013; 2(1):1.

(31) Lucas DJ, Sweeney JF, Pawlik TM. The timing of complications impacts risk of readmission after hepatopancreatobiliary surgery. *Surgery* 2014; 155(5):945-953.

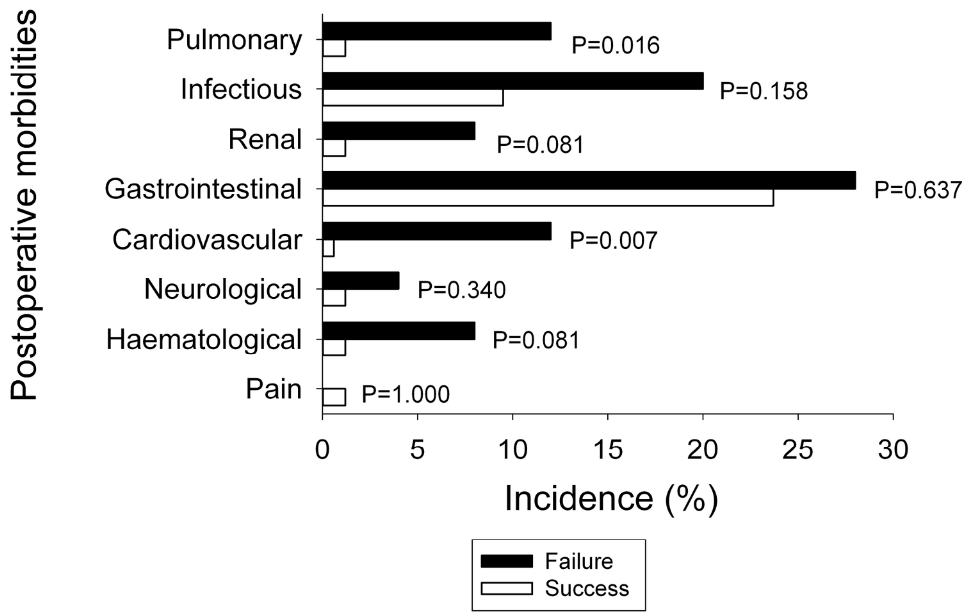
(32) Barton GR, Sach TH, Doherty M, et al. An assessment of the discriminative ability of the EQ-5Dindex, SF-6D, and EQ VAS, using sociodemographic factors and clinical conditions. *Eur J Health Econ* 2008; 9(3):237-249.

(33) Gianotti L, Beretta S, Luperto M, B et al. Enhanced recovery strategies in colorectal surgery: is the compliance with the whole program required to achieve the target? *Int J Colorectal Dis* 2014; 29(3):329-341.

(34) Nicholson A, Lowe MC, Parker J, et al. Systematic review and meta-analysis of enhanced recovery programmes in surgical patients. *Br J Surg* 2014; 101(3):172-188.

(35) Neville A, Lee L, Antonescu I, et al. Systematic review of outcomes used to evaluate enhanced recovery after surgery. *Br J Surg* 2014; 101(3):159-171.

Figure 1. The incidence of postoperative morbidities on the third day after surgery by enhanced recovery protocol groups. To control for type I error at 0.05 from multiple comparisons, P < 0.0063 was considered significant



The incidence of postoperative morbidities on the third day after surgery by enhanced recovery protocol groups. To control for type 1 error at 0.05 from multiple comparisons, P < 0.0063 was considered significant.
86x56mm (600 x 600 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9, Tables 2-4, footnotes
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	No missing data
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	9-10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	Text adequate
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 2
		(b) Indicate number of participants with missing data for each variable of interest	No missing data

		(c) Summarise follow-up time (eg, average and total amount)	10,11
Outcome data	15*	Report numbers of outcome events or summary measures over time	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 3 &4, 9,14-15
		(*b*) Report category boundaries when continuous variables were categorized	Tables footnotes
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	15
Discussion			
Key results	18	Summarise key results with reference to study objectives	15-18,19-20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Factors associated with failure of enhanced recovery protocol in patients undergoing major hepatobiliary and pancreatic surgery: a retrospective cohort study

Anna LEE[1], Chun Hung CHIU[1], Mui Wai Amy CHO[1], Charles David GOMERSALL[1], Kit Fai LEE[2], Yue Sun CHEUNG[2], Paul Bo San LAI[2]

[1] Department of Anaesthesia and Intensive Care, Prince of Wales Hospital, The Chinese University of Hong Kong

[2] Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Prince of Wales Hospital, The Chinese University of Hong Kong

Address for correspondence: Anna Lee, Department of Anaesthesia and Intensive Care, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong

Phone: +852 2632 2735 Fax: +852 2637 2422 Email: annalee@cuhk.edu.hk

Reprints: Reprints will not be available from the authors

Category: Research article

Meeting: Presented in part at the combined Royal Australasian College of Surgeons Annual Scientific Congress and the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine Annual Scientific Meeting, in Singapore, 5th-9th May 2014.

MESH terms: Enhanced recovery after surgery; Postoperative care; Liver surgery; Pancreatic surgery; Cohort

Word count: 251 (Abstract); 4083 (Main text, including tables and figures)

ABSTRACT

Objective: This study examined the risk factors associated with failure of enhanced recovery protocol after major hepatobiliary and pancreatic (HBP) surgery.

Setting and participants: A retrospective cohort of 194 adults patients undergoing major HBP surgery at a university hospital in Hong Kong was followed up for 30 days. The patients were from a larger cohort study of 736 consecutive adults with preoperative urinary cotinine concentration to examine the association between passive smoking and risk of perioperative respiratory complications and postoperative morbidities.

Outcome measures: The primary outcome was failure of enhanced recovery protocol. This was defined as a composite measure of the following events: intensive care unit (ICU) stay more than 24 hours after surgery, unplanned admission to ICU within 30 days after surgery, hospital readmission, reoperation and mortality.

Results: There were 25 failures of enhanced recovery after HBP surgery (12.9%, 95% CI, 8.5% to 18.4%). After adjusting for elective ICU admission, smokers (RR 2.21, 95% CI, 1.10 to 4.46), high preoperative alanine transaminase/glutamic-pyruvic transaminase (RR 3.55, 1.68 to 7.49) and postoperative morbidities (RR 2.69, 95% CI, 1.30 to 5.56) were associated with failures of enhanced recovery in the generalized estimating equation risk model. Compared to those managed successfully, failures stayed longer in ICU (median 19 *vs.* 25 hours, $P<0.001$) and in hospital for postoperative care (median 7 *vs.* 13 days, $P=0.003$).

Conclusion: Smokers and patients having high preoperative alanine transaminase/glutamic-pyruvic transaminase concentration or have a high risk of postoperative morbidities are likely to fail enhanced recovery protocol in HBP surgery programs.

Strengths and limitations of this study

- This is the first study to identify risk factors associated with the failure of enhanced recovery protocol in major hepatobiliary and pancreatic surgery.
- Instead of using length of hospital stay as an endpoint, failure was defined as a composite measure of slow recovery: length of stay in the intensive care unit (ICU) more than 24 hours after surgery, unplanned admission to ICU within 30 days, readmission to the hospital within 30 days after surgery, reoperation for complications and 30-day mortality
- Smokers (defined by self-reported history and adjusted urinary cotinine concentration) and patients having high preoperative alanine transaminase glutamic-pyruvic transaminase concentration or have a high risk of postoperative morbidities are likely to fail clinical pathways in fast-track hepatobiliary and pancreatic surgery. Similar results were found in a sensitivity analysis using adjusted urinary cotinine concentrations.
- We did not consider the compliance rate of individual components of the early recovery after hepatobiliary pancreatic surgery program
- High risk patients at risk of failing enhanced recovery protocols in major hepatobiliary pancreatic surgery may benefit from additional care to minimize perioperative morbidities and length of stay.

INTRODUCTION

Enhanced recovery after major hepatobiliary and pancreatic surgery (ERAHBPS) is a complex intervention that includes many of the following components: patient and family education, no bowel preparation, no preanaesthetic medication, preoperative carbohydrate loading, thromboembolic prophylaxis, antiemetic prophylaxis, epidural analgesia, intraoperative normothermia, prophylactic antibiotics, no systemic opioids, fluid restriction, no surgical drains, no standard postoperative nasogastric tubes, postoperative nutritional care and early mobilization.[1]

Recent systematic reviews[1;2] of several observational studies of ERAHBPS programs suggest that it is safe and feasible. Compared to traditional clinical pathways, fast-track hepatobiliary and pancreatic (HBP) surgery programs have similar risks of readmission, morbidity and mortality[1-3] and reduced the duration of postoperative length of stay and overall hospital cost.[3] However, compliance with core components of enhance recovery after liver surgery program vary between high-volume European centers, with a median adoption of 9 (range 7 to 12) of 22 core elements.[4]

As with all enhanced recovery after surgery (ERAS) programs, a small proportion of patients will fail fast-track HBP surgery and require additional intensive care unit (ICU) resources. Although not all fast-track HBP surgical patients are routinely admitted to ICU after their procedure,[5;6] ICU care after liver resection was associated with a decreased risk in hospital mortality (odds ratio 0.26, 95% CI 0.10 to 0.71) and a reduction in total hospital costs (13%).[7] These results suggest that careful selection of patients for ERAHBPS is crucial for maximizing the efficiency of perioperative care pathways.

Fast-track failure risk models after cardiac surgery have been developed[8] and externally validated[9] to facilitate the planning of perioperative care pathways, but factors associated with failure of enhanced recovery protocol after HBP surgery are unknown. The objectives of this study were to estimate the incidence of and identify the risk factors associated with failure of enhanced recovery protocol after HBP surgery. And with such information, we can identify a subgroup of patients at risk of failure to provide additional care to minimize perioperative morbidities and length of stay.

METHODS

Study cohort

The Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee approved this retrospective cohort study of patients undergoing major HBP surgery at the Prince of Wales Hospital in Hong Kong between January 2011 and November 2012 (CRE-2013.181). The patients were from a larger cohort study of 736 consecutive adult patients with preoperative urinary cotinine concentration to examine the association between passive smoking and risk of perioperative respiratory complications and postoperative morbidities.[10] All patients gave written informed consent before surgery. Patients undergoing other types of surgery, unable to give written informed consent, having chronic renal failure, younger than 18 years and urine cotinine samples collected more than 48 h before surgery were excluded.

The types of surgery included were laparoscopic liver resection (nonanatomical wedge resections, or resection of 1 or 2 segments), minor open liver resection (fewer than 3 segments including multiple non-anatomical resections), major open liver resections (3 or more segments), liver resection with biliary reconstruction[11;12] and pancreatic surgery. Pancreatic surgery included Whipple's procedure, double bypass (hepaticojejunostomy and gastrojejunostomy in unresectable cancer of the head of pancreas) and distal pancreatectomy.

Typical management

The typical clinical care pathway for HBP surgical patients involved the following: admission to surgical ward one day before surgery, patient education, no preanaesthetic medication, mechanical prophylaxis for deep vein thrombosis, intraoperative prophylactic antibiotics, normothermia during surgery, ICU or surgical ward for first 24 h after surgery, surgical ward, early mobilization and hospital discharge (Table 1). The use of epidural anaesthesia/analgesia is not routine because of concerns about postoperative coagulopathy in patients with cirrhosis of liver.[13] Patients were given patient controlled morphine analgesia.

Although there was no formalized extubation protocol, extubation at the end of liver resection surgery or within 1 h after admission to ICU was expected; for pancreatic surgery where most patients went to ICU, extubation within 4 h was expected. There is no surgical high dependency unit at the Prince of Wales Hospital, Hong Kong.

Drains were removed as soon as possible when there was no biliary or pancreatic anastomiotic leakage. In patients undergoing liver surgery, gradual resumption of diet from liquid to solid food was expected during the first three days after surgery. For Whipple's operation, the diet resumption was slower, starting from the fifth postoperative day and a normal diet was expected by the seventh. For patients who could not tolerate oral intake by the seventh day after surgery, parenteral nutrition was given with a target of 25-30kcal/kg.

Table 1. Enhanced recovery elements in liver and pancreatic resectional surgery

	Liver resection	**Pancreatic resection**
Pre-operatively	Information given to patient and patient education No premedication	Information given to patient and patient education No premedication
Day 0	Normothermia during surgery Mechanical prophylaxis for deep vein thrombosis Intraoperative prophylactic antibiotics No nasogastric tube No routine abdominal drain	Normothermia during surgery Mechanical prophylaxis for deep vein thrombosis Intraoperative prophylactic antibiotics Routine nasogastric and abdominal drain only for Whipple's operation
Day 1	Patient controlled morphine analgesia Oral fluid Moving patient to chair	Patient controlled morphine analgesia Oral fluid Moving patient to chair
Day 2	Fluid diet Enhanced mobilization Removal of urinary catheter	Enhanced mobilization
Day 3	Soft diet Removal of drain	Removal of urinary catheter Removal of nasogastric tube if draining <300ml
Day 4	Normal diet	Fluid diet Removal of drain
Day 5	Discharge if no fever, pain can be controlled with oral analgesics and patient has adequate mobilization	Soft diet
Day 6		Normal diet
Day 7		Discharge if no fever, pain can be controlled with oral analgesics and patient has adequate mobilization

Outcome Measure

For the purposes of this study, we define failure of enhanced recovery protocol after HBP surgery as a composite measure of the following events: length of ICU stay more than 24 h after surgery, unplanned admission to ICU within 30 days after surgery, readmission to the hospital within 30 days after surgery, reoperation for complications and 30-day mortality. These events were chosen as markers of slow recovery and are common quality of care indicators. Unlike previous ERAS studies, we did not chose length of stay as a primary outcome as it has been shown that reductions in length of stay up to a median of 2 days may be related to changes in organization of care and not to the effect of the ERAS program.[14]

We collected patient demographics, smoking status, preoperative urinary cotinine concentration that was adjusted for creatinine level, American Society of Anesthesiologists' Physical Status, Surgical Apgar score,[15] duration of surgery, ICU admission details, APACHE II (severity of illness score in patients admitted to ICU),[16] preoperative liver function tests, indocyanine green test and coagulation tests, and failure events from the hospital electronic Clinical Management System database. The research staff collected postoperative morbidities (pulmonary, infectious, renal, gastrointestinal, cardiovascular, neurological, haematological, wound and severe pain) on the third day after surgery using a reliable and valid Postoperative Morbidity Survey questionnaire.[17] The EQ-5D index, a health-related quality of life using a US set of reference weights, was measured on the third day after surgery[18] as the greatest difference in EQ-5D index between ERAHBPS and standard care occur between postoperative day 2 and 5.[19] 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] The research staff was blinded to the urinary cotinine concentration results.

Statistical Analysis

Continuous data were expressed as mean and standard deviation (SD) or median and interquartile range (IQR). The 95% confidence interval (95% CI) was estimated around the incidence of HBP surgery failure. Appropriate Student t-tests, Mann-Whitney U tests, χ^2 analyses or exact tests were used to compare factors associated with failure of enhanced recovery protocol. To adjust for multiple testing of individual postoperative morbidity events, a Bonferroni correction was used so that the significance criterion was set at $P<0.0063$. There was no missing data.

A generalized estimating equation (GEE) model with a Poisson distribution, log-link function and exchangeable correlation[20] was used to obtain a common-effect relative risk (RR) of failure of enhanced recovery protocol after HBP surgery. This GEE model was more appropriate for analysis of composite measures and assumes that there is a single common exposure effect across all components used in the failure composite endpoint. We included elective ICU admission in the model as we considered this factor to be clinically important with regards to postoperative bed utilization. The calibration and discrimination of the model was assessed using the Hosmer-Lemeshow goodness-of-fit test and estimating the area under the receiver characteristic operating curve (AUROC). Internal validation of the model was performed by bootstrapping 1000 samples and estimating the AUROC and 95% CI. A sensitivity analysis of the GEE model was performed by including adjusted urinary cotinine concentration as a continuous variable instead of smoking status as a categorical independent variable. Statistical analyses were performed using STATA (version 13.1) software (STATA Corp, College Station, TX).

Using PASS (version 11) software (NCSS, Kaysville, UT), a sample size of 190 (19 failure and 171 success) patients will achieve 80% power to detect a difference of 0.20 between the AUROC under the null hypothesis of 0.70 (fair discrimination) and an AUROC under the alternative hypothesis of 0.50 (no discrimination) using a 2-sided z-test at a significance level of 0.05.

RESULTS

Of the 217 consecutive patients undergoing HBP surgery, 23 were not eligible (10 not available in the ward at time of recruitment, 5 refusals, 4 already participated in the study, 3 unable to consent and 1 had renal impairment). There were 25 failures of enhanced recovery (12.9%, 95% CI, 8.5% to 18.4%) in 194 patients undergoing major HBP surgery. Of the 94 elective ICU patients, 10 (10.6%) stayed in ICU for more than 24 hours after surgery. One patient was admitted to ICU unexpectedly due to surgical emphysema and stayed in ICU for 43 hours after surgery. There were 2 (2.1%) readmissions to ICU within 24 hours (1 for acute renal failure/atrial fibrillation and 1 for atelectasis), 2 reoperations (1.0%) and 11 hospital readmissions (5.6%). The reasons for hospital readmissions were abdominal complications (n=5), wound complications (n=3), pyrexia with or without chills (n=2) and jaundice (n=1). No patient died within 30 days after surgery.

The median postoperative length of hospital stay was longer in the failure group (13 days, 7 to 18) than in the successful group (7 days, 6 to 9) (P=0.003). This was mainly due to longer median length of postoperative hospital stay in patients undergoing hepatic surgery failing enhanced recovery management (12 days, 7 to 17) compared to those successfully managed (7 days, 6 to 9) (P=0.001). There were 26 patients undergoing pancreatic surgery. The median duration of postoperative hospital stay in patients undergoing pancreatic surgery failing and succeeding enhanced recovery management were 16 (5 to 35) and 10 (8 to 18) days, respectively (P=0.716). The median time from initial hospital discharge to readmission was 6 days (2 to 13).

The demographic and preoperative characteristics associated with failure of enhanced recovery protocol are shown in Table 2. Of the 137 patients with preoperative indocyanine green test results, 14 (7.2%) were classified as borderline and 4 (2.1%) were poor. There was no significant association between indocyanine green test results and failure groups (P=0.735).

Table 2. Demographic and preoperative factors associated with failure of enhanced recovery protocol after major hepatobiliary and pancreatic surgery

	Enhanced Recovery Protocol Groups		
	Failure (n=25)	Success (n=169)	P value
Mean age (SD), y	57 (11)	59 (11)	0.498
Males, n (%)	19 (76)	131 (78)	0.866
American Society of Anesthesiologists' Physical Status, n (%)			
I	2 (8)	25 (15)	
II	18 (72)	121 (72)	0.512
III/IV	5 (20)	23 (14)	
Current smoker, n (%)	9 (36)	35 (21)	0.088
Median adjusted cotinine, ng/mL (IQR)	1.34 (0.60 – 265.82)	1.07 (0.55 – 3.51)	0.183
Type of Surgery, n (%)			
Exploratory	1 (4)	5 (3)	
Laparoscopic liver resection	3 (12)	28 (17)	
Minor open liver resection	5 (20)	62 (37)	0.441
Major open liver ± biliary reconstruction	12 (48)	52 (31)	
Whipple	2 (8)	15 (9)	
Other pancreatic surgery	2 (8)	7 (4)	
Magnitude of Surgery, n (%)			

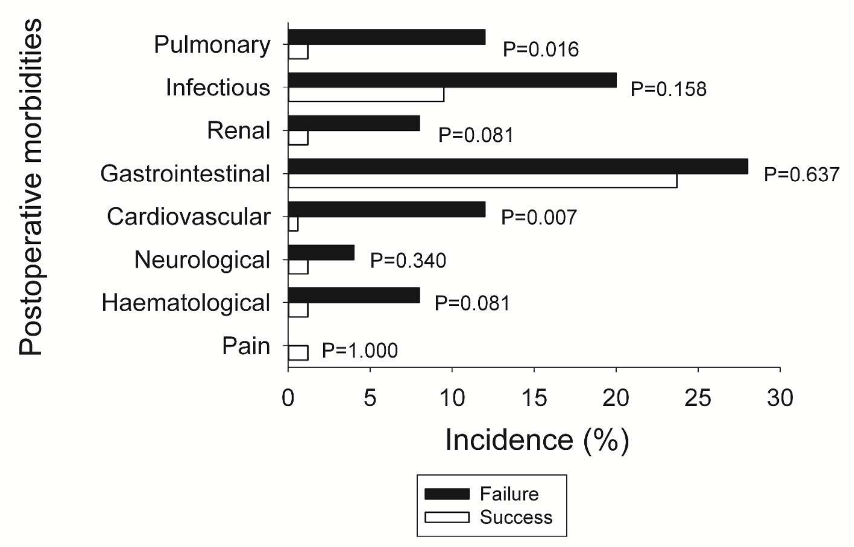
Major	4 (16)	36 (21)	0.541
Ultramajor	21 (84)	133 (79)	
Low albumin (<35 g/L), n (%)	2 (4)	12 (7)	0.698
High bilirubin (μmol/L)*, n(%)	7 (28)	27 (16)	0.159
Alkaline Phosphatase (IU/L), n (%)			
Normal†	14 (56)	123 (73)	
Low	1 (4)	3 (2)	0.214
High	10 (40)	43 (25)	
High ALT/GPT(IU/L)‡, n (%)	11 (44)	23 (14)	0.001
Haemoglobin (g/dL), n (%)			
Normal§	14 (56)	121 (72)	
Low	10 (40)	46 (27)	0.211
High	1 (4)	2 (1)	
Platelets, n (%)			
Normal (150-384 x 10^9/L)	14 (56)	117 (69)	
Low	10 (40)	50 (30)	0.294
High	1 (4)	2 (1)	
Prothrombin time, n (%)			
Normal (9.5-12 s)	19 (76)	144 (85)	
Low	0 (0)	1 (1)	0.423
High	6 (24)	24 (14)	
Activated partial thromboplastin time, n (%)			
Normal (28.2-37.4 s)	22 (88)	153 (91)	
Low	2 (8)	10 (6)	0.914
High	1 (4)	6 (4)	
High International Normalised Ratio, n (%)	0 (0)	2 (1)	1.000
Urinary Creatinine (μmol/L), n (%)			
Normal†	20 (80)	143 (85)	
Low	3 (12)	17 (10)	0.815
High	2 (8)	9 (5)	

*High bilirubin defined as more than 19μmol/L in males, and more than 17μmol/l in females
†Age and gender specific range
‡High Alanine transaminase/glutamic-pyruvic transaminase defined as more than 67 IU/L in males and more than 55 IU/L in females
§Normal range is 13.2 to 17.2g/dL for males and 11.9 to 15.1g/dL for females

The median duration of hepatic surgery was similar between failure (270 min, 186 to 336) and successful enhanced recovery groups (236 min, 180 to 315) (P=0.348). There was no difference in the median duration of pancreatic surgery between failure (395 min, 192 to 641) and successful enhanced recovery groups (488 min, 291 to 560) (P=0.933). The median Surgical Apgar Score was similar between failure (8, 6 to 9) and successful (8, 7 to 9) enhanced recovery groups (P=0.912).

Elective ICU admissions occurred in 13 (41.9%) patients undergoing laparoscopic liver resection, 19 (23.9%) minor open liver resection, 45 (70.3%) major open liver and/or biliary reconstruction, 15 (88.2%) Whipple and 2 (22.2%) other pancreatic surgery. Of the 94 elective ICU admissions, 17 (18.1%) patients failed enhanced recovery protocols after HBP surgery. Patients with elective ICU admissions were more likely to be enhanced recovery failures than patients sent to the ward after surgery ($RR_{unadjusted}$ 1.49, 95% CI, 1.09 to 2.05). The median duration of ICU length of stay was longer in the failure group (25 hours, 20 to 39) than in the successful enhanced recovery group (19 hours, 17 to 22) (P<0.001). However, the mean APACHE II score was similar between failure (13.6±3.8) and successful (12.3±3.5) enhanced recovery groups (P=0.150).

The overall incidence of postoperative morbidities was 35.1% (95% CI, 28.4% to 42.2%). There was no reported wound dehiscence (requiring surgical exploration or drainage of pus from the operation wound with or without isolation of organisms)[17] on the third postoperative day. There was no difference in the incidence of postoperative morbidities between groups according to the *a priori* Bonferroni-correction P value criterion (Figure 1). Patients with a postoperative morbidity were twice as likely to be a failure ($RR_{unadjusted}$ 2.36, 95% CI, 1.13 to 4.91) than those without. There was no difference in the mean EQ-5D index between failure (0.53 ± 0.30) and successful enhanced recovery groups (0.63 ± 0.29) (P=0.166).



After adjusting for planned postoperative ICU care, current smoking, high preoperative alanine transaminase/glutamic-pyruvic transaminase concentration and postoperative morbidities on the third day after surgery were significant risk factors associated with failure of enhanced recovery protocol (Table 3). The GEE model had adequate calibration (Hosmer-Lemeshow goodness-of-fit χ^2 8df, P=0.352) and excellent discrimination (AUROC = 0.87, 95% CI, 0.83 to 0.92).

Table 3. Risk factors for failure in enhanced recovery protocol after major hepatobiliary and pancreatic surgery using the generalized estimating equation model

	Common-effect RR (95% CI)	**P value**
ICU admission		
None	1.00	
Elective	0.41 (0.14 – 1.20)	0.104
Smoking status		
Never-smoker/Exsmoker	1.00	
Current smoker	2.21 (1.10 – 4.46)	0.027
ALT/GPT(IU/L)*		
Normal	1.00	
High	3.55 (1.68 – 7.49)	0.001
Any postoperative morbidity		
None	1.00	
Present on Day 3	2.69 (1.30 – 5.56)	0.007

*High Alanine transaminase/glutamic-pyruvic transaminase defined as more than 67 IU/L in males and more than 55 IU/L in females

The results of a sensitivity analysis on the main GEE model using adjusted urinary cotinine concentration instead of smoking status are shown Table 4. Compared to patients with nil urinary cotinine concentration, the predicted adjusted risk for failure in enhanced recovery protocol in patients with urinary cotinine concentrations of 50, 500 and 1500 ng/ml were 1.04 (95% CI, 1.01 to 1.07), 1.52 (95% CI, 1.22 to 1.90) and 3.51 (95% CI, 1.80 to 6.83) respectively. The GEE model had adequate calibration (Hosmer-Lemeshow goodness-of-fit χ^2 8df, P=0.496) and excellent discrimination (AUROC = 0.87, 95% CI, 0.82 to 0.91).

Table 4. Sensitivity analysis on the risk factors for failure in enhanced recovery protocol after major hepatobiliary and pancreatic surgery

	Common-effect RR (95% CI)	P value
ICU admission		
None	1.000	
Elective	0.505 (0.176 – 1.444)	0.202
Adjusted cotinine concentration (ng/ml)*	1.001 (1.000 – 1.001)	<0.001
ALT/GPT(IU/L)†		
Normal	1.000	
High	4.626 (2.097 – 10.207)	<0.001
Any postoperative morbidity		
None	1.000	
Present on Day 3	2.657 (1.312 – 5.379)	0.007

*Active smokers commonly defined as urinary cotinine concentration >50ng/ml[21]
†High Alanine transaminase/glutamic-pyruvic transaminase defined as more than 67 IU/L in males and more than 55 IU/L in females

DISCUSSION

Our management of patients undergoing HBP surgery incorporated a small proportion of evidence-based components described in ERAS programs for hepatic[4] and pancreatic[22] surgery. For every eight patients undergoing major HBP surgery, one was at risk of failing enhanced recovery protocols in major HBP surgery. However, no patients died within 30 days after surgery. 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. Prolonged stay in ICU (12%) and hospital readmissions (6%) were the most common failure events. Our hospital readmission rate and 30-day mortality are within the range described in studies included in recent systematic reviews of fast-track liver resection and pancreatic surgery.[1;2;22;23] Our patients who failed enhanced recovery protocols after major HBP surgery had clinically significantly longer ICU stays and postoperative stays in hospital.

Access to ICU admission after surgery affects outcomes.[24] Under half (48.5%) of our patients had elective ICU admission after surgery. Patients with elective ICU admissions after surgery were high-risk patients as suggested by the results of the univariate analysis where they were 1.5 times more likely to be failures than patients sent to the ward after surgery. However, when the elective ICU admission variable was included in the GEE models, the common-effect relative risk, although not significant, suggested a possible protective effect on failure. A previous study showed that intensive care physician staffing was associated with better outcomes after hepatic resection from prompt diagnosis and treatment of nonsurgical complications.[7] Our incidence of ICU readmission (2.1%) within 24 h appears acceptable. Previous studies included in systematic reviews of fast-track HBP surgery[1;2;22;23] have not reported the rate of ICU readmissions.

There is a paucity of studies examining the effect of smoking on fast-track surgery. Compared to conventional care programs, smoking was associated with 30-day hospital readmissions (odds ratio 1.60, 95% CI, 1.05 to 2.44), but not with prolonged length of hospital stay of more than 4 days (odds ratio 1.34, 95% CI, 0.92 to 1.95) in patients undergoing fast-track hip and knee arthroplasty.[25] However, current smoking was based on self-reported smoking history up to a month before hospital[25] and the effect of smoking on enhanced recovery failure is likely to be underestimated as many smokers (17%) deny smoking before elective surgery.[26] In contrast, we used both self-reported smoking history and adjusted urinary cotinine concentration to increase the accuracy of preoperative smoking status data. We have shown that current smokers were up to four times more likely to be enhanced recovery failures compared to never-smokers and former smokers in the GEE model. The results of the sensitivity analysis using adjusted urinary cotinine concentration further strengthens the association between smoking and the risk of enhanced recovery failure. Thus, smoking cessation before HBP surgery would be expected to decrease the risk of enhanced recovery failures substantially. Smoking cessation at least 4 weeks, and preferably 8 weeks, before surgery significantly reduced the risk of postoperative respiratory and wound-healing complications.[27] Smoking is a modifiable risk factor that surgeons and anaesthesiologists can work on when patients are booked for surgery.

Of all the preoperative liver function and coagulation tests performed, high alanine transaminase/glutamic-pyruvic transaminases (ALT/GPT) concentration was the only independent biochemical risk factor associated with enhanced recovery failures. The strong association is indicative of the high risk of operating on an acutely inflamed liver.[28] A previous study[29] found that alanine aminotransferase ≥70 IU/L was an independent risk factor (odd ratio 2.02, 95% CI, 1.33 to 3.07) for postoperative complications after hepatic resection for hepatocellular carcinoma.

Fast-track open liver resection was associated with a reduction in general complications as defined by the Postoperative Morbidity Survey[17] by 36% (95% CI

16% to 52%).[19] A direct comparison between our incidence of postoperative morbidities on the third day after surgery and Jones et al.'s study[19] is difficult as the timing of their postoperative morbidities was not specified. Our GEE model found that patients with any postoperative morbidity on the third day after surgery were three times more likely to be an enhanced recovery failure than patients without reported postoperative morbidity. Specifically, after adjustment for multiple testing, cardiovascular events (diagnostic tests or treatment in last 24 h for new myocardial infarction or ischaemia, hypotension, arrhythmias, cardiogenic pulmonary oedema or thrombotic events)[17] was weakly associated with the risk of failure. Early postoperative morbidities are associated with longer duration of hospital stay[30] and an increased risk of hospital readmission.[31]

Using a minimal important difference of 0.03,[32] we found that patients in the enhanced recovery failure group had lower health-related quality of life than in the successful group. Our health-related quality of life on the third day after surgery in the successful group was similar to those reported in the standard care group by Jones et al.[19] Our practice does not include carbohydrate drink up to 2 hours before surgery, pharmacological prophylaxis for deep vein thrombosis or the routine use of epidural anaesthesia.

Overall, the results of this study suggest that it is possible to identify a subgroup of patients requiring additional care to minimize perioperative morbidity and length of stay. Patients who are smokers, have high ALT/GPT concentration or are at a high risk of postoperative morbidities are likely to fail enhanced recovery protocol in HBP surgery. In defining who is at high risk of postoperative morbidities, the American

Society of Anesthesiologists' Physical Status grades III and IV and risk more than 50% estimated in the POSSUM-defined postoperative morbidity model may be useful as surrogate markers.[17] For those patients at high risk of HBP surgery failure, elective postoperative ICU admission and measures targeted to avoid postoperative cardiorespiratory complications are warranted to reduce the risk of failure of enhanced recovery events.

There are several limitations of this study. First, we did not measure the compliance rate of individual components of the ERAHBPS program. Recent studies suggest that 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] Second, the common-effects GEE analysis was influenced by the higher frequencies of prolonged ICU length of stay (12%) and hospital readmissions (6%) events than other components included in the definition of failure. Our sample size was small for the use an average relative-effect GEE analysis[20] to address this problem. There is a potential for residual confounding despite the use of multivariate analyses in this cohort study. The applicability of the identified risk factors to select patients suitable for ERAHBPS programs in other settings requires further validation. Finally, the failure outcomes were limited to the early to intermediate phases of recovery; we did not measure outpatient complications[31] or late recovery outcomes, such as functional status and health-related quality of life beyond one month as recommended recently by Neville et al.[35]

In conclusion, patients who smoked, had elevated preoperative ALT/GPT or experienced postoperative morbidities were at risk of failing enhanced recovery protocols in major HBP surgery and may benefit from additional care. Patients who failed enhanced recovery protocols in HBP surgery stayed in ICU and in the hospital longer.

Acknowledgements

Funding Support: The work was substantially supported by the Health and Health Services Research Fund, Food and Health Bureau, Hong Kong SAR Government (Grant number: 08090311). The funding source had no role in the design, conduct or analysis of the study, or in the decision to submit the manuscript for publication.

Competing Interests: None declared.

Ethics approval: The Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee approved this cohort study of patients undergoing major HBP surgery at the Prince of Wales Hospital in Hong Kong between January 2011 and November 2012 (CRE-2013.181).

Contributors: AL performed the statistical analyses and had full access to all the data in the study. AL drafted the manuscript and made substantial revisions. All authors were involved in the study concept and design of the study. CHC collected the data. AL, MWAC, CDC, KFL, YSC and BSPL interpreted the data. All authors made critical revisions of the manuscript for important intellectual content and approved the final version of the manuscript. AL is guarantor.

Data sharing: No additional data available

Provenance and peer review: Not commissioned, externally peer reviewed.

References

(1) Spelt L, Ansari D, Sturesson C, Tingstedt B, Andersson R. Fast-track programmes for hepatopancreatic resections: where do we stand? *HPB (Oxford)* 2011; 13(12):833-838.

(2) Hall TC, Dennison AR, Bilku DK, Metcalfe MS, Garcea G. Enhanced recovery programmes in hepatobiliary and pancreatic surgery: a systematic review. *Ann R Coll Surg Engl* 2012; 94(5):318-326.

(3) Lin DX, Li X, Ye QW, Lin F, Li LL, Zhang QY. Implementation of a fast-track clinical pathway decreases postoperative length of stay and hospital charges for liver resection. *Cell Biochem Biophys* 2011; 61(2):413-419.

(4) Wong-Lun-Hing EM, van Dam RM, Heijnen LA, Busch OR, Terkivatan T, van HR et al. Is Current Perioperative Practice in Hepatic Surgery Based on Enhanced Recovery After Surgery (ERAS) Principles? *World J Surg* 2013.

(5) Schultz NA, Larsen PN, Klarskov B, Plum LM, Frederiksen HJ, Christensen BM et al. Evaluation of a fast-track programme for patients undergoing liver resection. *Br J Surg* 2013; 100(1):138-143.

(6) Sanchez-Perez B, Aranda-Narvaez JM, Suarez-Munoz MA, Eladel-Delfresno M, Fernandez-Aguilar JL, Perez-Daga JA et al. Fast-track program in laparoscopic liver surgery: Theory or fact? *World J Gastrointest Surg* 2012; 4(11):246-250.

(7) Dimick JB, Pronovost PJ, Lipsett PA. The Effect of ICU Physician Staffing and Hospital Volume on Outcomes After Hepatic Resection. *J Intens Care Med* 2002; 17:41-47.

(8) Constantinides VA, Tekkis PP, Fazil A, Kaur K, Leonard R, Platt M et al. Fast-track failure after cardiac surgery: development of a prediction model. *Crit Care Med* 2006; 34(12):2875-2882.

(9) Lee A, Zhu F, Underwood MJ, Gomersall CD. Fast-track failure after cardiac surgery: external model validation and implications to ICU bed utilization. *Crit Care Med* 2013; 41(5):1205-1213.

(10) Lee A, Chui PT, Chiu CH, Tan PE, Tam TP, Samy W et al. Risk of perioperative respiratory complications and postoperative morbidity in a cohort of adults exposed to passive smoking. *Ann Surg* 2014; Feb 6 [epub ahead].

(11) Lee KF, Cheung YS, Chong CN, Tsang YY, Ng WW, Ling E et al. Laparoscopic versus open hepatectomy for liver tumours: a case control study. *Hong Kong Med J* 2007; 13(6):442-448.

(12) Lee KF, Cheung YS, Wong J, Chong CC, Wong JS, Lai PB. Randomized clinical trial of open hepatectomy with or without intermittent Pringle manoeuvre. *Br J Surg* 2012; 99(9):1203-1209.

(13) Shontz R, Karuparthy V, Temple R, Brennan TJ. Prevalence and risk factors predisposing to coagulopathy in patients receiving epidural analgesia for hepatic surgery. *Reg Anesth Pain Med* 2009; 34(4):308-311.

(14) Maessen JM, Dejong CH, Kessels AG, von Meyenfeldt MF. Length of stay: an inappropriate readout of the success of enhanced recovery programs. *World J Surg* 2008; 32(6):971-975.

(15) Reynolds PQ, Sanders NW, Schildcrout JS, Mercaldo ND, St Jacques PJ. Expansion of the surgical Apgar score across all surgical subspecialties as a means to predict postoperative mortality. *Anesthesiology* 2011; 114(6):1305-1312.

(16) Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; 13(10):818-829.

(17) Grocott MP, Browne JP, Van der Meulen J, Matejowsky C, Mutch M, Hamilton MA et al. The Postoperative Morbidity Survey was validated and used to describe morbidity after major surgery. *J Clin Epidemiol* 2007; 60(9):919-928.

(18) Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. *Med Care* 2005; 43(3):203-220.

(19) Jones C, Kelliher L, Dickinson M, Riga A, Worthington T, Scott MJ et al. Randomized clinical trial on enhanced recovery versus standard care following open liver resection. *Br J Surg* 2013; 100(8):1015-1024.

(20) Mascha EJ, Sessler DI. Statistical grand rounds: design and analysis of studies with binary- event composite endpoints: guidelines for anesthesia research. *Anesth Analg* 2011; 112(6):1461-1471.

(21) SRNT Subcommittee on biochemical verification. Biochemical verification of tobacco use and cessation. *Nicotine Tob Res* 2002; 4(2):149-159.

(22) Coolsen MM, van Dam RM, van der Wilt AA, Slim K, Lassen K, Dejong CH. Systematic review and meta-analysis of enhanced recovery after pancreatic surgery with particular emphasis on pancreaticoduodenectomies. *World J Surg* 2013; 37(8):1909-1918.

(23) Coolsen MM, Wong-Lun-Hing EM, van Dam RM, van der Wilt AA, Slim K, Lassen K et al. A systematic review of outcomes in patients undergoing liver surgery in an enhanced recovery after surgery pathways. *HPB (Oxford)* 2013; 15(4):245-251.

(24) Pearse RM, Moreno RP, Bauer P, Pelosi P, Metnitz P, Spies C et al. Mortality after surgery in Europe: a 7 day cohort study. *Lancet* 2012; 380(9847):1059-1065.

(25) Jorgensen CC, Kehlet H. Outcomes in smokers and alcohol users after fast-track hip and knee arthroplasty. *Acta Anaesthesiol Scand* 2013; 57(5):631-638.

(26) Lee A, Gin T, Chui PT, Tan PE, Chiu CH, Tam TP et al. The accuracy of urinary cotinine immunoassay test strip as an add-on test to self-reported smoking before major elective surgery. *Nicotine Tob Res* 2013; 15(10):1690-1695.

(27) Wong J, Lam DP, Abrishami A, Chan MT, Chung F. Short-term preoperative smoking cessation and postoperative complications: a systematic review and meta-analysis. *Can J Anaesth* 2012; 59(3):268-279.

(28) Schroeder RA, Marroquin CE, Bute BP, Khuri S, Henderson WG, Kuo PC. Predictive indices of morbidity and mortality after liver resection. *Ann Surg* 2006; 243(3):373-379.

(29) Taketomi A, Kitagawa D, Itoh S, Harimoto N, Yamashita Y, Gion T et al. Trends in morbidity and mortality after hepatic resection for hepatocellular carcinoma: an institute's experience with 625 patients. *J Am Coll Surg* 2007; 204(4):580-587.

(30) Davies SJ, Francis J, Dilley J, Wilson RJ, Howell SJ, Allgar V. Measuring outcomes after major abdominal surgery during hospitalization: reliability and validity of the Postoperative Morbidity Survey. *Perioper Med (Lond)* 2013; 2(1):1.

(31) Lucas DJ, Sweeney JF, Pawlik TM. The timing of complications impacts risk of readmission after hepatopancreatobiliary surgery. *Surgery* 2014; 155(5):945-953.

(32) Barton GR, Sach TH, Doherty M, Avery AJ, Jenkinson C, Muir KR. An assessment of the discriminative ability of the EQ-5Dindex, SF-6D, and EQ VAS, using sociodemographic factors and clinical conditions. *Eur J Health Econ* 2008; 9(3):237-249.

(33) Gianotti L, Beretta S, Luperto M, Bernasconi D, Valsecchi MG, Braga M. Enhanced recovery strategies in colorectal surgery: is the compliance with the whole program required to achieve the target? *Int J Colorectal Dis* 2014; 29(3):329-341.

(34) Nicholson A, Lowe MC, Parker J, Lewis SR, Alderson P, Smith AF. Systematic review and meta-analysis of enhanced recovery programmes in surgical patients. *Br J Surg* 2014; 101(3):172-188.

(35) Neville A, Lee L, Antonescu I, Mayo NE, Vassiliou MC, Fried GM et al. Systematic review of outcomes used to evaluate enhanced recovery after surgery. *Br J Surg* 2014; 101(3):159-171.

Figure 1. The incidence of postoperative morbidities on the third day after surgery by enhanced recovery protocol groups. To control for type I error at 0.05 from multiple comparisons, $P < 0.0063$ was considered significant