

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-005330
Article Type:	Research
Date Submitted by the Author:	24-Mar-2014
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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

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Manuscripts

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3 **Factors associated with failure of enhanced recovery protocol in patients**
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5 **undergoing major hepatobiliary and pancreatic surgery: a cohort study**
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38 **Reprints:** Reprints will not be available from the authors
39

40 **Category:** Research article
41

42
43 **Meeting:** Will be presented in part at the combined Royal Australasian College of
44 Surgeons Annual Scientific Congress and the Australian and New Zealand College
45 of Anaesthetists and Faculty of Pain Medicine Annual Scientific Meeting, in
46 Singapore, 5th-9th May 2014.
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51 **MESH terms:** Enhanced recovery after surgery; Postoperative care; Liver surgery;
52 Pancreatic surgery; Cohort
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56 **Word count:** 245 (abstract); 3043 (text)
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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

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3 careful selection of patients for ERAHBPS is crucial for maximizing the efficiency of
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5 perioperative care pathways.
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10 Fast-track failure risk models after cardiac surgery have been developed[8] and
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12 externally validated[9] to facilitate the planning of perioperative care pathways, but
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14 factors associated with failure of enhanced recovery protocol after HBP surgery are
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16 unknown. The objectives of this study were to estimate the incidence of and identify
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18 the risk factors associated with failure of enhanced recovery protocol after HBP
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20 surgery. And with such information, we can identify a subgroup of patients at risk of
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22 failure to provide additional care to minimize perioperative morbidities and length of
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24 stay.
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28 29 **METHODS**

30 31 **Study cohort**

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34 The Joint Chinese University of Hong Kong-New Territories East Cluster Clinical
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36 Research Ethics Committee approved this cohort study of patients undergoing major
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38 HBP surgery at the Prince of Wales Hospital in Hong Kong between January 2011
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40 and November 2012 (CRE-2013.181). The patients were from a larger cohort study
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42 of 736 consecutive adult patients with preoperative urinary cotinine concentration to
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44 examine the association between passive smoking and risk of perioperative
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46 respiratory complications and postoperative morbidities.[10] All patients gave written
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48 informed consent before surgery. Patients undergoing other types of surgery, unable
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50 to give written informed consent, having chronic renal failure, younger than 18 years
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52 and urine cotinine samples collected more than 48 h before surgery were excluded.
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3 The types of surgery included were laparoscopic liver resection (nonanatomical
4 wedge resections, or resection of 1 or 2 segments), minor open liver resection (fewer
5 than 3 segments including multiple non-anatomical resections), major open liver
6 resections (3 or more segments), liver resection with biliary reconstruction[11,12]
7 and pancreatic surgery. Pancreatic surgery included Whipple procedure, double
8 bypass (hepaticojejunostomy and gastrojejunostomy in unresectable cancer of the
9 head of pancreas) and distal pancreatectomy.
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20 21 **Typical management**

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

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3 an adjusted urinary cotinine concentration ≥ 550 ng/mL within 48 hours before
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5 surgery.[10] The research staff was blinded to the urinary cotinine concentration
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7 results.
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10 11 12 **Statistical Analysis**

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14 Continuous data were expressed as mean and standard deviation (SD) or median
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16 and interquartile range (IQR). The 95% confidence interval (95% CI) was estimated
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18 around the incidence of HBP surgery failure. Appropriate Student t-tests, Mann-
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20 Whitney U tests, χ^2 analyses or exact tests were used to compare factors associated
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22 with failure of enhanced recovery protocol. To adjust for multiple testing of individual
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24 postoperative morbidity events, a Bonferroni correction was used so that the
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26 significance criterion was set at $P < 0.0063$. There was no missing data.
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32 A generalized estimating equation (GEE) model with a Poisson distribution, log-link
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34 function and exchangeable correlation[19] was used to obtain a common-effect
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36 relative risk (RR) of failure of enhanced recovery protocol after HBP surgery. This
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38 GEE model was more appropriate for analysis of composite measures and assumes
39
40 that there is a single common exposure effect across all components used in the
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42 failure composite endpoint. We included elective ICU admission in the model as we
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44 considered this factor to be clinically important with regards to postoperative bed
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46 utilization. The calibration and discrimination of the model was assessed using the
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48 Hosmer-Lemeshow goodness-of-fit test and estimating the area under the receiver
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50 characteristic operating curve (AUROC). Internal validation of the model was
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52 performed by bootstrapping 1000 samples and estimating the AUROC and 95% CI.
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3 Statistical analyses were performed using STATA (version 13.1) software (STATA
4 Corp, College Station, TX).
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10 Using PASS (version 11) software (NCSS, Kaysville, UT), a sample size of 190 (19
11 failure and 171 success) patients will achieve 80% power to detect a difference of
12 0.20 between the AUROC under the null hypothesis of 0.70 (fair discrimination) and
13 an AUROC under the alternative hypothesis of 0.50 (no discrimination) using a 2-
14 sided z-test at a significance level of 0.05.
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23 RESULTS

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25 Of the 217 consecutive patients undergoing HBP surgery, 23 were not eligible (10
26 not available in the ward at time of recruitment, 5 refusals, 4 already participated in
27 the study, 3 unable to consent and 1 had renal impairment). There were 25 failures
28 of enhanced recovery (12.9%, 95% CI, 8.5% to 18.4%) in 194 patients undergoing
29 major HBP surgery. Of the 94 elective ICU patients, 10 (10.6%) stayed in ICU for
30 more than 24 hours after surgery. One patient was admitted to ICU unexpectedly
31 due to surgical emphysema and stayed in ICU for 43 hours after surgery. There were
32 2 (2.1%) readmissions to ICU within 24 hours (1 for acute renal failure/atrial
33 fibrillation and 1 for atelectasis), 2 reoperations (1.0%) and 11 hospital readmissions
34 (11.6%). No patient died within 30 days after surgery.
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50 The median postoperative length of hospital stay was longer in the failure group (13
51 days, 7 to 18) than in the successful group (7 days, 6 to 9) (P=0.003). This was
52 mainly due to longer median length of postoperative hospital stay in patients
53 undergoing hepatic surgery failing enhanced recovery management (12 days, 7 to
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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		P value
	Failure (n=25)	Success (n=169)	
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)	0.512
II	18 (72)	121 (72)	
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)	0.441
Laparoscopic liver resection	3 (12)	28 (17)	
Minor open liver resection	5 (20)	62 (37)	
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 ($\mu\text{mol/L}$)*, 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

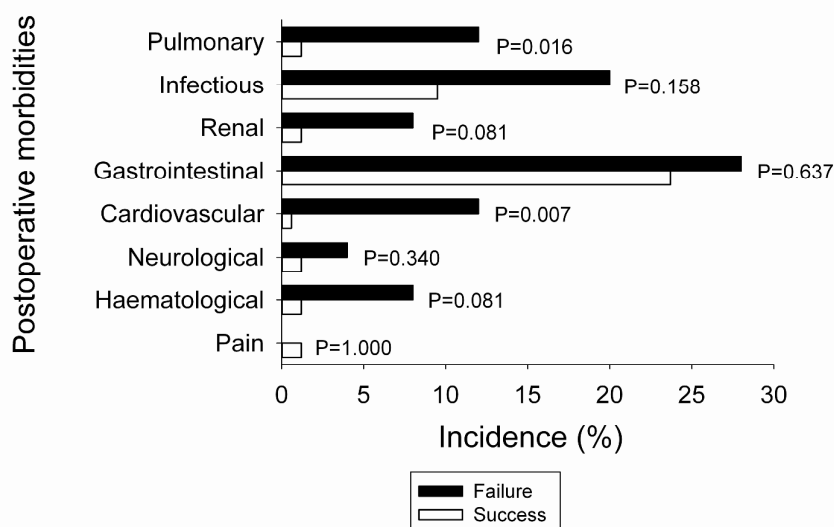
The median duration of hepatic surgery was similar between failure (270 min, 186 to 336) and successful enhanced recovery groups (236 min, 180 to 315) (P=0.348).

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.

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3 Our hospital readmission rate and 30-day mortality are within the range described in
4 studies included in recent systematic reviews of fast-track liver resection and
5 pancreatic surgery.[1,2,20,21] Our patients who failed enhanced recovery protocols
6 after major HBP surgery had clinically significantly longer ICU stays and
7 postoperative stays in hospital.
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16 Under half (48.5%) of our patients had elective ICU admission after surgery. Patients
17 with elective ICU admissions after surgery were high-risk patients as suggested by
18 the results of the univariate analysis where they were 1.5 times more likely to be
19 failures than patients sent to the ward after surgery. However, when the elective ICU
20 admission variable was included in the GEE model, the common-effect relative risk,
21 although not significant ($P=0.104$), suggested a possible protective effect on failure.
22
23 A previous study showed that intensive care physician staffing was associated with
24 better outcomes after hepatic resection from prompt diagnosis and treatment of
25 nonsurgical complications.[7] Our incidence of ICU readmission (2.1%) within 24 h
26 appears acceptable. Previous studies included in systematic reviews of fast-track
27 HBP surgery[1,2,20,21] have not reported the rate of ICU readmissions.
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43 There is a paucity of studies examining the effect of smoking on fast-track surgery.
44 Compared to conventional care programs, smoking was associated with 30-day
45 hospital readmissions (odds ratio 1.60, 95% CI, 1.05 to 2.44), but not with prolonged
46 length of hospital stay of more than 4 days (odds ratio 1.34, 95% CI, 0.92 to 1.95) in
47 patients undergoing fast-track hip and knee arthroplasty.[22] However, current
48 smoking was based on self-reported smoking history up to a month before
49 hospital[22] and the effect of smoking on enhanced recovery failure is likely to be
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3 underestimated as many smokers (17%) deny smoking before elective surgery.[23]
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5 In contrast, we used both self-reported smoking history and adjusted urinary cotinine
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7 concentration to increase the accuracy of preoperative smoking status data. We
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9 have shown that current smokers were up to four times more likely to be enhanced
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11 recovery failures compared to never-smokers and former smokers in the GEE model.
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13 Thus, smoking cessation before HBP surgery would be expected to decrease the
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15 risk of enhanced recovery failures substantially. Smoking cessation at least 4 weeks,
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17 and preferably 8 weeks, before surgery significantly reduced the risk of postoperative
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19 respiratory and wound-healing complications.[24] Smoking is a modifiable risk factor
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21 that surgeons and anaesthesiologists can work on when patients are booked for
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23 surgery.
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30 Of all the preoperative liver function and coagulation tests performed, high alanine
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32 transaminase/glutamic-pyruvic transaminases (ALT/GPT) concentration was the only
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34 independent biochemical risk factor associated with enhanced recovery failures. The
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36 strong association is indicative of the high risk of operating on an acutely inflamed
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38 liver.[25] A previous study[26] found that alanine aminotransferase ≥ 70 IU/L was an
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40 independent risk factor (odd ratio 2.02, 95% CI, 1.33 to 3.07) for postoperative
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42 complications after hepatic resection for hepatocellular carcinoma.
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48 Fast-track open liver resection was associated with a reduction in general
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50 complications as defined by the Postoperative Morbidity Survey[16] by 36% (95% CI
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52 16% to 52%).[18] A direct comparison between our incidence of postoperative
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54 morbidities on the third day after surgery and Jones et al.'s study[18] is difficult as
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56 the timing of their postoperative morbidities was not specified. Our GEE model found
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3 that patients with any postoperative morbidity on the third day after surgery were
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5 three times more likely to be an enhanced recovery failure than patients without
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7 reported postoperative morbidity. Specifically, after adjustment for multiple testing,
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9 cardiovascular events (diagnostic tests or treatment in last 24 h for new myocardial
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11 infarction or ischaemia, hypotension, arrhythmias, cardiogenic pulmonary oedema or
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13 thrombotic events)[16] was weakly associated with the risk of failure.
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19 Using a minimal important difference of 0.03,[27] we found that patients in the
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21 enhanced recovery failure group had lower health-related quality of life than in the
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23 successful group. Our health-related quality of life on the third day after surgery in
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25 the successful group was similar to those reported in the standard care group by
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27 Jones et al.[18] Our practice does not include carbohydrate drink up to 2 hours
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29 before surgery, pharmacological prophylaxis for deep vein thrombosis or the routine
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31 use of epidural anaesthesia.
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37 Overall, the results of this study suggest that it is possible to identify a subgroup of
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39 patients requiring additional care to minimize perioperative morbidity and length of
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41 stay. Patients who are smokers, have high ALT/GPT concentration or are at a high
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43 risk of postoperative morbidities are likely to fail enhanced recovery protocol in HBP
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45 surgery. In defining who is at high risk of postoperative morbidities, the American
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47 Society of Anesthesiologists' Physical Status grades III and IV and risk more than 50%
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49 estimated in the POSSUM-defined postoperative morbidity model may be useful as
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51 surrogate markers.[16] For those patients at high risk of HBP surgery failure, elective
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53 postoperative ICU admission and measures targeted to avoid postoperative
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3 cardiorespiratory complications are warranted to reduce the risk of failure of
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5 enhanced recovery events.
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10 There are several limitations of this study. First, we did not measure the compliance
11 rate of individual components of the ERAHBPS program. Recent studies suggest
12 that better patient care and outcome can be achieved regardless of the number, the
13 combination, the type, and the strength of evidence of the individual ERAS
14 component.[28,29] Second, the common-effects GEE analysis was influenced by the
15 higher frequencies of prolonged ICU length of stay (12%) and hospital readmissions
16 (6%) events than other components included in the definition of failure. Our sample
17 size was small for the use an average relative-effect GEE analysis[19] to address
18 this problem. There is a potential for residual confounding despite the use of
19 multivariate analyses in this cohort study. The applicability of the identified risk
20 factors to select patients suitable for ERAHBPS programs in other settings requires
21 further validation. Finally, the failure outcomes were limited to the early to
22 intermediate phases of recovery; we did not measure late recovery outcomes, such
23 as functional status and health-related quality of life beyond one month as
24 recommended recently by Neville et al.[30]
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45 In conclusion, patients who smoked, had elevated preoperative ALT/GPT or
46 experienced postoperative morbidities were at risk of failing enhanced recovery
47 protocols in major HBP surgery and may benefit from additional care. Patients who
48 failed enhanced recovery protocols in HBP surgery stayed in ICU and in the hospital
49 longer.
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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.

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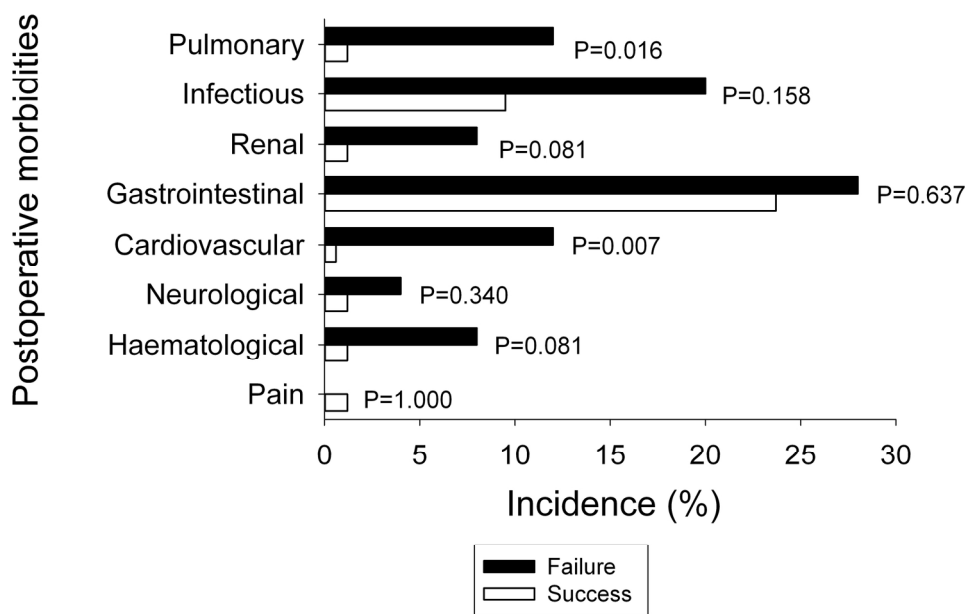
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Figure 1. The incidence of postoperative morbidities on the third day after surgery by enhanced recovery protocol groups. To control for type I error at 0.05 from multiple comparisons, $P < 0.0063$ was considered significant

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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)

view only

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:	<i>BMJ Open</i>
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

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3 **Factors associated with failure of enhanced recovery protocol in patients**
4 **undergoing major hepatobiliary and pancreatic surgery: a retrospective cohort**
5 **study**
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39 **Reprints:** Reprints will not be available from the authors
40

41
42 **Category:** Research article
43

44
45 **Meeting:** Presented in part at the combined Royal Australasian College of Surgeons
46 Annual Scientific Congress and the Australian and New Zealand College of
47 Anaesthetists and Faculty of Pain Medicine Annual Scientific Meeting, in Singapore,
48 5th-9th May 2014.
49
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52 **MESH terms:** Enhanced recovery after surgery; Postoperative care; Liver surgery;
53 Pancreatic surgery; Cohort
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57 **Word count:** 251 (Abstract); 4083 (Main text, including tables and figures)
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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 mortality¹⁻³ 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

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3 of patients for ERAHBPS is crucial for maximizing the efficiency of perioperative care
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5 pathways.
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10 Fast-track failure risk models after cardiac surgery have been developed⁸ and
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12 externally validated⁹ to facilitate the planning of perioperative care pathways, but
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14 factors associated with failure of enhanced recovery protocol after HBP surgery are
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16 unknown. The objectives of this study were to estimate the incidence of and identify
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18 the risk factors associated with failure of enhanced recovery protocol after HBP
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20 surgery. And with such information, we can identify a subgroup of patients at risk of
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22 failure to provide additional care to minimize perioperative morbidities and length of
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24 stay.
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28 29 **METHODS**

30 31 **Study cohort**

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33 The Joint Chinese University of Hong Kong-New Territories East Cluster Clinical
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35 Research Ethics Committee approved this retrospective cohort study of patients
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37 undergoing major HBP surgery at the Prince of Wales Hospital in Hong Kong
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39 between January 2011 and November 2012 (CRE-2013.181). The patients were
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41 from a larger cohort study of 736 consecutive adult patients with preoperative urinary
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43 cotinine concentration to examine the association between passive smoking and risk
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45 of perioperative respiratory complications and postoperative morbidities.¹⁰ All
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47 patients gave written informed consent before surgery. Patients undergoing other
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49 types of surgery, unable to give written informed consent, having chronic renal failure,
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51 younger than 18 years and urine cotinine samples collected more than 48 h before
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53 surgery were excluded.
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5 The types of surgery included were laparoscopic liver resection (nonanatomical
6 wedge resections, or resection of 1 or 2 segments), minor open liver resection (fewer
7 than 3 segments including multiple non-anatomical resections), major open liver
8 resections (3 or more segments), liver resection with biliary reconstruction^{11;12} and
9 pancreatic surgery. Pancreatic surgery included Whipple's procedure, double bypass
10 (hepaticojejunostomy and gastrojejunostomy in unresectable cancer of the head of
11 pancreas) and distal pancreatectomy.
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21 22 23 **Typical management**

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25 The typical clinical care pathway for HBP surgical patients involved the following:
26 admission to surgical ward one day before surgery, patient education, no
27 preanaesthetic medication, mechanical prophylaxis for deep vein thrombosis,
28 intraoperative prophylactic antibiotics, normothermia during surgery, ICU or surgical
29 ward for first 24 h after surgery, surgical ward, early mobilization and hospital
30 discharge (Table 1). The use of epidural anaesthesia/analgesia is not routine
31 because of concerns about postoperative coagulopathy in patients with cirrhosis of
32 liver.¹³ Patients were given patient controlled morphine analgesia.
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45 Although there was no formalized extubation protocol, extubation at the end of liver
46 resection surgery or within 1 h after admission to ICU was expected; for pancreatic
47 surgery where most patients went to ICU, extubation within 4 h was expected. There
48 is no surgical high dependency unit at the Prince of Wales Hospital, Hong Kong.
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Drains were removed as soon as possible when there was no biliary or pancreatic anastomotic 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 surgery¹⁸ 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

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3 cotinine concentration ≥ 550 ng/mL within 48 hours before surgery.¹⁰ The research
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5 staff was blinded to the urinary cotinine concentration results.
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8 9 10 **Statistical Analysis**

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12 Continuous data were expressed as mean and standard deviation (SD) or median
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14 and interquartile range (IQR). The 95% confidence interval (95% CI) was estimated
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16 around the incidence of HBP surgery failure. Appropriate Student t-tests, Mann-
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18 Whitney U tests, χ^2 analyses or exact tests were used to compare factors associated
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20 with failure of enhanced recovery protocol. To adjust for multiple testing of individual
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22 postoperative morbidity events, a Bonferroni correction was used so that the
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24 significance criterion was set at $P < 0.0063$. There was no missing data.
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30 A generalized estimating equation (GEE) model with a Poisson distribution, log-link
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32 function and exchangeable correlation²⁰ was used to obtain a common-effect relative
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34 risk (RR) of failure of enhanced recovery protocol after HBP surgery. This GEE
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36 model was more appropriate for analysis of composite measures and assumes that
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38 there is a single common exposure effect across all components used in the failure
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40 composite endpoint. We included elective ICU admission in the model as we
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42 considered this factor to be clinically important with regards to postoperative bed
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44 utilization. The calibration and discrimination of the model was assessed using the
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46 Hosmer-Lemeshow goodness-of-fit test and estimating the area under the receiver
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48 characteristic operating curve (AUROC). Internal validation of the model was
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50 performed by bootstrapping 1000 samples and estimating the AUROC and 95% CI.
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53 A sensitivity analysis of the GEE model was performed by including adjusted urinary
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55 cotinine concentration as a continuous variable instead of smoking status as a
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3 categorical independent variable. Statistical analyses were performed using STATA
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5 (version 13.1) software (STATA Corp, College Station, TX).
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10 Using PASS (version 11) software (NCSS, Kaysville, UT), a sample size of 190 (19
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12 failure and 171 success) patients will achieve 80% power to detect a difference of
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14 0.20 between the AUROC under the null hypothesis of 0.70 (fair discrimination) and
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16 an AUROC under the alternative hypothesis of 0.50 (no discrimination) using a 2-
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18 sided z-test at a significance level of 0.05.
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20 21 22 **RESULTS**

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24 Of the 217 consecutive patients undergoing HBP surgery, 23 were not eligible (10
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26 not available in the ward at time of recruitment, 5 refusals, 4 already participated in
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28 the study, 3 unable to consent and 1 had renal impairment). There were 25 failures
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30 of enhanced recovery (12.9%, 95% CI, 8.5% to 18.4%) in 194 patients undergoing
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32 major HBP surgery. Of the 94 elective ICU patients, 10 (10.6%) stayed in ICU for
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34 more than 24 hours after surgery. One patient was admitted to ICU unexpectedly
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36 due to surgical emphysema and stayed in ICU for 43 hours after surgery. There were
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38 2 (2.1%) readmissions to ICU within 24 hours (1 for acute renal failure/atrial
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40 fibrillation and 1 for atelectasis), 2 reoperations (1.0%) and 11 hospital readmissions
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42 (5.6%). The reasons for hospital readmissions were abdominal complications (n=5),
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44 wound complications (n=3), pyrexia with or without chills (n=2) and jaundice (n=1).
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48 No patient died within 30 days after surgery.
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54 The median postoperative length of hospital stay was longer in the failure group (13
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56 days, 7 to 18) than in the successful group (7 days, 6 to 9) (P=0.003). This was
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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		P value
	Failure (n=25)	Success (n=169)	
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)	0.512
II	18 (72)	121 (72)	
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)	0.441
Laparoscopic liver resection	3 (12)	28 (17)	
Minor open liver resection	5 (20)	62 (37)	
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 ($\mu\text{mol/L}$)*, 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 ($\mu\text{mol/L}$), n (%)			
Normal [†]	20 (80)	143 (85)	
Low	3 (12)	17 (10)	0.815
High	2 (8)	9 (5)	

*High bilirubin defined as more than 19 $\mu\text{mol/L}$ in males, and more than 17 $\mu\text{mol/L}$ 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

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3 and/or biliary reconstruction, 15 (88.2%) Whipple and 2 (22.2%) other pancreatic
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5 surgery. Of the 94 elective ICU admissions, 17 (18.1%) patients failed enhanced
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7 recovery protocols after HBP surgery. Patients with elective ICU admissions were
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9 more likely to be enhanced recovery failures than patients sent to the ward after
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11 surgery ($RR_{unadjusted}$ 1.49, 95% CI, 1.09 to 2.05). The median duration of ICU length
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13 of stay was longer in the failure group (25 hours, 20 to 39) than in the successful
14
15 enhanced recovery group (19 hours, 17 to 22) ($P < 0.001$). However, the mean
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17 APACHE II score was similar between failure (13.6 ± 3.8) and successful (12.3 ± 3.5)
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19 enhanced recovery groups ($P = 0.150$).
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25 The overall incidence of postoperative morbidities was 35.1% (95% CI, 28.4% to
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27 42.2%). There was no reported wound dehiscence (requiring surgical exploration or
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29 drainage of pus from the operation wound with or without isolation of organisms)¹⁷ on
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31 the third postoperative day. There was no difference in the incidence of
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33 postoperative morbidities between groups according to the *a priori* Bonferroni-
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35 correction P value criterion (Figure 1). Patients with a postoperative morbidity were
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37 twice as likely to be a failure ($RR_{unadjusted}$ 2.36, 95% CI, 1.13 to 4.91) than those
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39 without. There was no difference in the mean EQ-5D index between failure ($0.53 \pm$
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41 0.30) and successful enhanced recovery groups (0.63 ± 0.29) ($P = 0.166$).
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50 After adjusting for planned postoperative ICU care, current smoking, high
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52 preoperative alanine transaminase/glutamic-pyruvic transaminase concentration and
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54 postoperative morbidities on the third day after surgery were significant risk factors
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56 associated with failure of enhanced recovery protocol (Table 3). The GEE model had
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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
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Active smokers commonly defined as urinary cotinine concentration >50ng/ml²¹

[†]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 hepatic⁴ and pancreatic²² 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

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3 showed that intensive care physician staffing was associated with better outcomes
4 after hepatic resection from prompt diagnosis and treatment of nonsurgical
5 complications.⁷ Our incidence of ICU readmission (2.1%) within 24 h appears
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7 acceptable. Previous studies included in systematic reviews of fast-track HBP
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9 surgery^{1;2;22;23} have not reported the rate of ICU readmissions.
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16 There is a paucity of studies examining the effect of smoking on fast-track surgery.
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18 Compared to conventional care programs, smoking was associated with 30-day
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20 hospital readmissions (odds ratio 1.60, 95% CI, 1.05 to 2.44), but not with prolonged
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22 length of hospital stay of more than 4 days (odds ratio 1.34, 95% CI, 0.92 to 1.95) in
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24 patients undergoing fast-track hip and knee arthroplasty.²⁵ However, current smoking
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26 was based on self-reported smoking history up to a month before hospital²⁵ and the
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28 effect of smoking on enhanced recovery failure is likely to be underestimated as
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30 many smokers (17%) deny smoking before elective surgery.²⁶ In contrast, we used
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32 both self-reported smoking history and adjusted urinary cotinine concentration to
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34 increase the accuracy of preoperative smoking status data. We have shown that
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36 current smokers were up to four times more likely to be enhanced recovery failures
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38 compared to never-smokers and former smokers in the GEE model. The results of
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40 the sensitivity analysis using adjusted urinary cotinine concentration further
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42 strengthens the association between smoking and the risk of enhanced recovery
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44 failure. Thus, smoking cessation before HBP surgery would be expected to decrease
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46 the risk of enhanced recovery failures substantially. Smoking cessation at least 4
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48 weeks, and preferably 8 weeks, before surgery significantly reduced the risk of
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50 postoperative respiratory and wound-healing complications.²⁷ Smoking is a
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3 modifiable risk factor that surgeons and anaesthesiologists can work on when
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5 patients are booked for surgery.
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10 Of all the preoperative liver function and coagulation tests performed, high alanine
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12 transaminase/glutamic-pyruvic transaminases (ALT/GPT) concentration was the only
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14 independent biochemical risk factor associated with enhanced recovery failures. The
15
16 strong association is indicative of the high risk of operating on an acutely inflamed
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18 liver.²⁸ A previous study²⁹ found that alanine aminotransferase ≥ 70 IU/L was an
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20 independent risk factor (odd ratio 2.02, 95% CI, 1.33 to 3.07) for postoperative
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22 complications after hepatic resection for hepatocellular carcinoma.
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27 Fast-track open liver resection was associated with a reduction in general
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29 complications as defined by the Postoperative Morbidity Survey¹⁷ by 36% (95% CI
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31 16% to 52%).¹⁹ A direct comparison between our incidence of postoperative
32
33 morbidities on the third day after surgery and Jones et al.'s study¹⁹ is difficult as the
34
35 timing of their postoperative morbidities was not specified. Our GEE model found
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37 that patients with any postoperative morbidity on the third day after surgery were
38
39 three times more likely to be an enhanced recovery failure than patients without
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41 reported postoperative morbidity. Specifically, after adjustment for multiple testing,
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43 cardiovascular events (diagnostic tests or treatment in last 24 h for new myocardial
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45 infarction or ischaemia, hypotension, arrhythmias, cardiogenic pulmonary oedema or
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47 thrombotic events)¹⁷ was weakly associated with the risk of failure. Early
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49 postoperative morbidities are associated with longer duration of hospital stay³⁰ and
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51 an increased risk of hospital readmission.³¹
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3 Using a minimal important difference of 0.03,³² we found that patients in the
4
5 enhanced recovery failure group had lower health-related quality of life than in the
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7 successful group. Our health-related quality of life on the third day after surgery in
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9 the successful group was similar to those reported in the standard care group by
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11 Jones et al.¹⁹ Our practice does not include carbohydrate drink up to 2 hours before
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13 surgery, pharmacological prophylaxis for deep vein thrombosis or the routine use of
14
15 epidural anaesthesia.
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21 Overall, the results of this study suggest that it is possible to identify a subgroup of
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23 patients requiring additional care to minimize perioperative morbidity and length of
24
25 stay. Patients who are smokers, have high ALT/GPT concentration or are at a high
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27 risk of postoperative morbidities are likely to fail enhanced recovery protocol in HBP
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29 surgery. In defining who is at high risk of postoperative morbidities, the American
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31 Society of Anesthesiologists' Physical Status grades III and IV and risk more than 50%
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33 estimated in the POSSUM-defined postoperative morbidity model may be useful as
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35 surrogate markers.¹⁷ For those patients at high risk of HBP surgery failure, elective
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37 postoperative ICU admission and measures targeted to avoid postoperative
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39 cardiorespiratory complications are warranted to reduce the risk of failure of
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41 enhanced recovery events.
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48 There are several limitations of this study. First, we did not measure the compliance
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50 rate of individual components of the ERAHBPS program. Recent studies suggest
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52 that better patient care and outcome can be achieved regardless of the number, the
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54 combination, the type, and the strength of evidence of the individual ERAS
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56 component.^{33;34} Second, the common-effects GEE analysis was influenced by the
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3 higher frequencies of prolonged ICU length of stay (12%) and hospital readmissions
4 (6%) events than other components included in the definition of failure. Our sample
5 size was small for the use an average relative-effect GEE analysis²⁰ to address this
6 problem. There is a potential for residual confounding despite the use of multivariate
7 analyses in this cohort study. The applicability of the identified risk factors to select
8 patients suitable for ERAHBPS programs in other settings requires further validation.
9
10 Finally, the failure outcomes were limited to the early to intermediate phases of
11 recovery; we did not measure outpatient complications³¹ or late recovery outcomes,
12 such as functional status and health-related quality of life beyond one month as
13 recommended recently by Neville et al.³⁵
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28 In conclusion, patients who smoked, had elevated preoperative ALT/GPT or
29 experienced postoperative morbidities were at risk of failing enhanced recovery
30 protocols in major HBP surgery and may benefit from additional care. Patients who
31 failed enhanced recovery protocols in HBP surgery stayed in ICU and in the hospital
32 longer.
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41 **Acknowledgements**

42
43 **Funding Support:** The work was substantially supported by the Health and Health
44 Services Research Fund, Food and Health Bureau, Hong Kong SAR Government
45 (Grant number: 08090311). The funding source had no role in the design, conduct or
46 analysis of the study, or in the decision to submit the manuscript for publication.
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52 **Competing Interests:** None declared.
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54 **Ethics approval:** The Joint Chinese University of Hong Kong-New Territories East
55 Cluster Clinical Research Ethics Committee approved this cohort study of patients
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3 undergoing major HBP surgery at the Prince of Wales Hospital in Hong Kong
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5 between January 2011 and November 2012 (CRE-2013.181).
6

7 **Contributors:** AL performed the statistical analyses and had full access to all the
8 data in the study. AL drafted the manuscript and made substantial revisions. All
9 authors were involved in the study concept and design of the study. CHC collected
10 the data. AL, MWAC, CDC, KFL, YSC and BSPL interpreted the data. All authors
11 made critical revisions of the manuscript for important intellectual content and
12 approved the final version of the manuscript. AL is guarantor.
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20 **Data sharing:** No additional data available
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22 **Provenance and peer review:** Not commissioned, externally peer reviewed.
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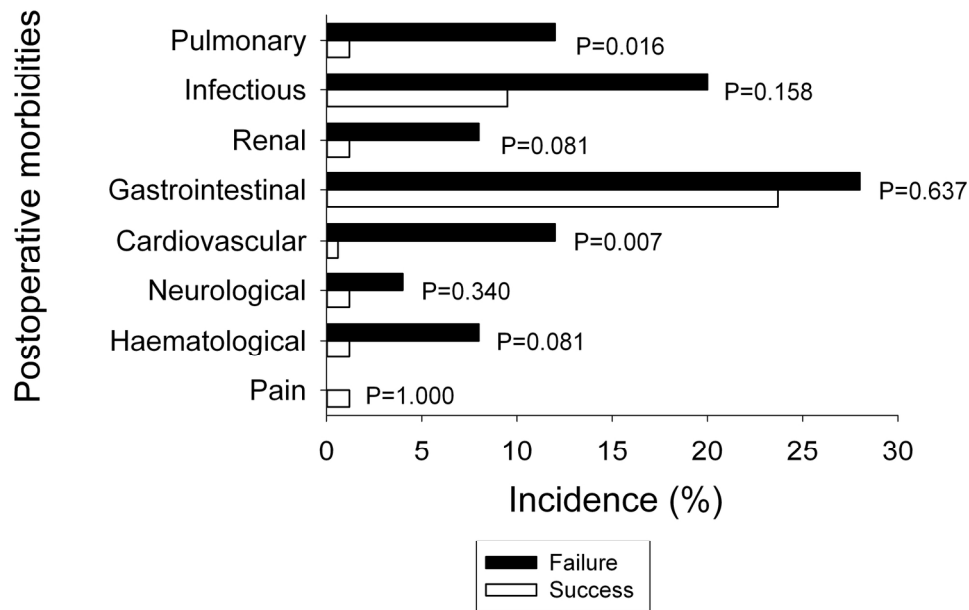
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3 Figure 1. The incidence of postoperative morbidities on the third day after surgery by
4 enhanced recovery protocol groups. To control for type I error at 0.05 from multiple
5 comparisons, $P < 0.0063$ was considered significant
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29 The incidence of postoperative morbidities on the third day after surgery by enhanced recovery protocol
30 groups. To control for type 1 error at 0.05 from multiple comparisons, $P < 0.0063$ was considered
31 significant.

32 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>.

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3 **Factors associated with failure of enhanced recovery protocol in patients**
4 **undergoing major hepatobiliary and pancreatic surgery: a retrospective cohort**
5 **study**
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11 Anna LEE¹ , Chun Hung CHIU¹ , Mui Wai Amy CHO¹ , Charles David

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13 GOMERSALL¹ , Kit Fai LEE² , Yue Sun CHEUNG² , Paul Bo San LAI²
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39 **Reprints:** Reprints will not be available from the authors
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41 **Category:** Research article
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43 **Meeting:** Presented in part at the combined Royal Australasian College of Surgeons
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45 Annual Scientific Congress and the Australian and New Zealand College of
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47 Anaesthetists and Faculty of Pain Medicine Annual Scientific Meeting, in Singapore,
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49 5th-9th May 2014.
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52 **MESH terms:** Enhanced recovery after surgery; Postoperative care; Liver surgery;
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54 Pancreatic surgery; Cohort
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56 **Word count:** 251 (Abstract); 4083 (Main text, including tables and figures)
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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 mortality¹⁻³ 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

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3 of patients for ERAHBPS is crucial for maximizing the efficiency of perioperative care
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5 pathways.
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10 Fast-track failure risk models after cardiac surgery have been developed⁸ and
11 externally validated⁹ to facilitate the planning of perioperative care pathways, but
12 factors associated with failure of enhanced recovery protocol after HBP surgery are
13 unknown. The objectives of this study were to estimate the incidence of and identify
14 the risk factors associated with failure of enhanced recovery protocol after HBP
15 surgery. And with such information, we can identify a subgroup of patients at risk of
16 failure to provide additional care to minimize perioperative morbidities and length of
17 stay.
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28 29 30 **METHODS**

31 32 **Study cohort**

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34 The Joint Chinese University of Hong Kong-New Territories East Cluster Clinical
35 Research Ethics Committee approved this retrospective cohort study of patients
36 undergoing major HBP surgery at the Prince of Wales Hospital in Hong Kong
37 between January 2011 and November 2012 (CRE-2013.181). The patients were
38 from a larger cohort study of 736 consecutive adult patients with preoperative urinary
39 cotinine concentration to examine the association between passive smoking and risk
40 of perioperative respiratory complications and postoperative morbidities.¹⁰ All
41 patients gave written informed consent before surgery. Patients undergoing other
42 types of surgery, unable to give written informed consent, having chronic renal failure,
43 younger than 18 years and urine cotinine samples collected more than 48 h before
44 surgery were excluded.
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5 The types of surgery included were laparoscopic liver resection (nonanatomical
6 wedge resections, or resection of 1 or 2 segments), minor open liver resection (fewer
7 than 3 segments including multiple non-anatomical resections), major open liver
8 resections (3 or more segments), liver resection with biliary reconstruction^{11;12} and
9 pancreatic surgery. Pancreatic surgery included Whipple's procedure, double bypass
10 (hepaticojejunostomy and gastrojejunostomy in unresectable cancer of the head of
11 pancreas) and distal pancreatectomy.
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21 22 23 **Typical management**

24 The typical clinical care pathway for HBP surgical patients involved the following:
25 admission to surgical ward one day before surgery, patient education, no
26 preanaesthetic medication, mechanical prophylaxis for deep vein thrombosis,
27 intraoperative prophylactic antibiotics, normothermia during surgery, ICU or surgical
28 ward for first 24 h after surgery, surgical ward, early mobilization and hospital
29 discharge (Table 1). The use of epidural anaesthesia/analgesia is not routine
30 because of concerns about postoperative coagulopathy in patients with cirrhosis of
31 liver.¹³ Patients were given patient controlled morphine analgesia.
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45 Although there was no formalized extubation protocol, extubation at the end of liver
46 resection surgery or within 1 h after admission to ICU was expected; for pancreatic
47 surgery where most patients went to ICU, extubation within 4 h was expected. There
48 is no surgical high dependency unit at the Prince of Wales Hospital, Hong Kong.
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Drains were removed as soon as possible when there was no biliary or pancreatic anastomotic 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 surgery¹⁸ 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

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3 cotinine concentration ≥ 550 ng/mL within 48 hours before surgery.¹⁰ The research
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5 staff was blinded to the urinary cotinine concentration results.
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8 9 10 **Statistical Analysis**

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12 Continuous data were expressed as mean and standard deviation (SD) or median
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14 and interquartile range (IQR). The 95% confidence interval (95% CI) was estimated
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16 around the incidence of HBP surgery failure. Appropriate Student t-tests, Mann-
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18 Whitney U tests, χ^2 analyses or exact tests were used to compare factors associated
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20 with failure of enhanced recovery protocol. To adjust for multiple testing of individual
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22 postoperative morbidity events, a Bonferroni correction was used so that the
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24 significance criterion was set at $P < 0.0063$. There was no missing data.
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30 A generalized estimating equation (GEE) model with a Poisson distribution, log-link
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32 function and exchangeable correlation²⁰ was used to obtain a common-effect relative
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34 risk (RR) of failure of enhanced recovery protocol after HBP surgery. This GEE
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36 model was more appropriate for analysis of composite measures and assumes that
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38 there is a single common exposure effect across all components used in the failure
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40 composite endpoint. We included elective ICU admission in the model as we
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42 considered this factor to be clinically important with regards to postoperative bed
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44 utilization. The calibration and discrimination of the model was assessed using the
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46 Hosmer-Lemeshow goodness-of-fit test and estimating the area under the receiver
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48 characteristic operating curve (AUROC). Internal validation of the model was
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50 performed by bootstrapping 1000 samples and estimating the AUROC and 95% CI.
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54 **A sensitivity analysis of the GEE model was performed by including adjusted urinary**
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56 **cotinine concentration as a continuous variable instead of smoking status as a**
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3 **categorical independent variable.** Statistical analyses were performed using STATA
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5 (version 13.1) software (STATA Corp, College Station, TX).
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10 Using PASS (version 11) software (NCSS, Kaysville, UT), a sample size of 190 (19
11 failure and 171 success) patients will achieve 80% power to detect a difference of
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13 0.20 between the AUROC under the null hypothesis of 0.70 (fair discrimination) and
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15 an AUROC under the alternative hypothesis of 0.50 (no discrimination) using a 2-
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17 sided z-test at a significance level of 0.05.
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20 21 22 **RESULTS**

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24 Of the 217 consecutive patients undergoing HBP surgery, 23 were not eligible (10
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26 not available in the ward at time of recruitment, 5 refusals, 4 already participated in
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28 the study, 3 unable to consent and 1 had renal impairment). There were 25 failures
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30 of enhanced recovery (12.9%, 95% CI, 8.5% to 18.4%) in 194 patients undergoing
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32 major HBP surgery. Of the 94 elective ICU patients, 10 (10.6%) stayed in ICU for
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34 more than 24 hours after surgery. One patient was admitted to ICU unexpectedly
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36 due to surgical emphysema and stayed in ICU for 43 hours after surgery. There were
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38 2 (2.1%) readmissions to ICU within 24 hours (1 for acute renal failure/atrial
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40 fibrillation and 1 for atelectasis), 2 reoperations (1.0%) and 11 hospital readmissions
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42 (5.6%). **The reasons for hospital readmissions were abdominal complications (n=5),**
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44 **wound complications (n=3), pyrexia with or without chills (n=2) and jaundice (n=1).**
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49 No patient died within 30 days after surgery.
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54 The median postoperative length of hospital stay was longer in the failure group (13
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56 days, 7 to 18) than in the successful group (7 days, 6 to 9) (P=0.003). This was
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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		P value
	Failure (n=25)	Success (n=169)	
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)	0.512
II	18 (72)	121 (72)	
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)	0.441
Laparoscopic liver resection	3 (12)	28 (17)	
Minor open liver resection	5 (20)	62 (37)	
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 (%)			

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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 ($\mu\text{mol/L}$)*, 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 ($\mu\text{mol/L}$), n (%)			
Normal [†]	20 (80)	143 (85)	
Low	3 (12)	17 (10)	0.815
High	2 (8)	9 (5)	

*High bilirubin defined as more than 19 $\mu\text{mol/L}$ in males, and more than 17 $\mu\text{mol/L}$ 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

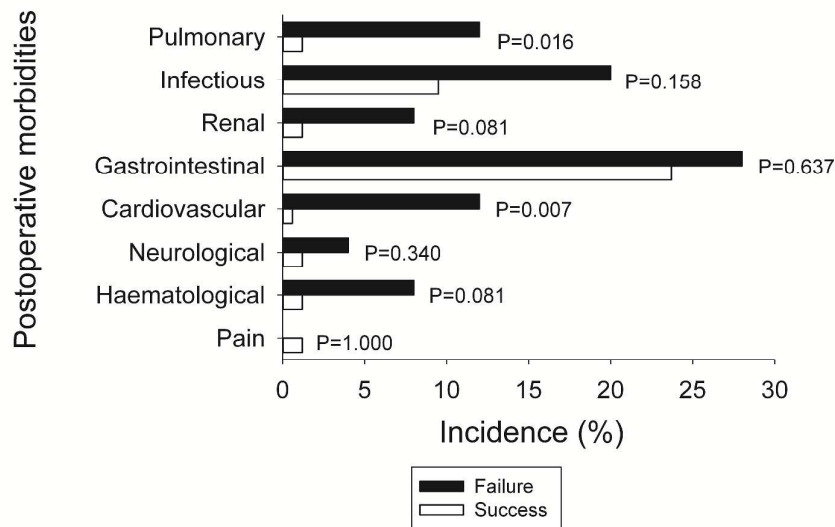
The median duration of hepatic surgery was similar between failure (270 min, 186 to 336) and successful enhanced recovery groups (236 min, 180 to 315) (P=0.348).

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

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3 and/or biliary reconstruction, 15 (88.2%) Whipple and 2 (22.2%) other pancreatic
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5 surgery. Of the 94 elective ICU admissions, 17 (18.1%) patients failed enhanced
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7 recovery protocols after HBP surgery. Patients with elective ICU admissions were
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9 more likely to be enhanced recovery failures than patients sent to the ward after
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11 surgery ($RR_{unadjusted}$ 1.49, 95% CI, 1.09 to 2.05). The median duration of ICU length
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13 of stay was longer in the failure group (25 hours, 20 to 39) than in the successful
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15 enhanced recovery group (19 hours, 17 to 22) ($P < 0.001$). However, the mean
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17 APACHE II score was similar between failure (13.6 ± 3.8) and successful (12.3 ± 3.5)
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19 enhanced recovery groups ($P = 0.150$).
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25 The overall incidence of postoperative morbidities was 35.1% (95% CI, 28.4% to
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27 42.2%). There was no reported wound dehiscence (requiring surgical exploration or
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29 drainage of pus from the operation wound with or without isolation of organisms)¹⁷ on
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31 the third postoperative day. There was no difference in the incidence of
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33 postoperative morbidities between groups according to the *a priori* Bonferroni-
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35 correction P value criterion (Figure 1). Patients with a postoperative morbidity were
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37 twice as likely to be a failure ($RR_{unadjusted}$ 2.36, 95% CI, 1.13 to 4.91) than those
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39 without. There was no difference in the mean EQ-5D index between failure ($0.53 \pm$
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41 0.30) and successful enhanced recovery groups (0.63 ± 0.29) ($P = 0.166$).
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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/ml²¹

†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 hepatic⁴ and pancreatic²² 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

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3 readmission rate and 30-day mortality are within the range described in studies
4 included in recent systematic reviews of fast-track liver resection and pancreatic
5 surgery.^{1;2;22;23} Our patients who failed enhanced recovery protocols after major HBP
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8 surgery had clinically significantly longer ICU stays and postoperative stays in
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11 hospital.
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16 **Access to ICU admission after surgery affects outcomes.**²⁴ Under half (48.5%) of our
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18 patients had elective ICU admission after surgery. Patients with elective ICU
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20 admissions after surgery were high-risk patients as suggested by the results of the
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22 univariate analysis where they were 1.5 times more likely to be failures than patients
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24 sent to the ward after surgery. However, when the elective ICU admission variable
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26 was included in the GEE models, the common-effect relative risk, although not
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28 significant, suggested a possible protective effect on failure. A previous study
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30 showed that intensive care physician staffing was associated with better outcomes
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32 after hepatic resection from prompt diagnosis and treatment of nonsurgical
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34 complications.⁷ Our incidence of ICU readmission (2.1%) within 24 h appears
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36 acceptable. Previous studies included in systematic reviews of fast-track HBP
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38 surgery^{1;2;22;23} have not reported the rate of ICU readmissions.
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46 There is a paucity of studies examining the effect of smoking on fast-track surgery.
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48 Compared to conventional care programs, smoking was associated with 30-day
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50 hospital readmissions (odds ratio 1.60, 95% CI, 1.05 to 2.44), but not with prolonged
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52 length of hospital stay of more than 4 days (odds ratio 1.34, 95% CI, 0.92 to 1.95) in
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54 patients undergoing fast-track hip and knee arthroplasty.²⁵ However, current smoking
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56 was based on self-reported smoking history up to a month before hospital²⁵ and the
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3 effect of smoking on enhanced recovery failure is likely to be underestimated as
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5 many smokers (17%) deny smoking before elective surgery.²⁶ In contrast, we used
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7 both self-reported smoking history and adjusted urinary cotinine concentration to
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9 increase the accuracy of preoperative smoking status data. We have shown that
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11 current smokers were up to four times more likely to be enhanced recovery failures
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13 compared to never-smokers and former smokers in the GEE model. **The results of**
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15 **the sensitivity analysis using adjusted urinary cotinine concentration further**
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17 **strengthens the association between smoking and the risk of enhanced recovery**
18
19 **failure.** Thus, smoking cessation before HBP surgery would be expected to decrease
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21 the risk of enhanced recovery failures substantially. Smoking cessation at least 4
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23 weeks, and preferably 8 weeks, before surgery significantly reduced the risk of
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25 postoperative respiratory and wound-healing complications.²⁷ Smoking is a
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27 modifiable risk factor that surgeons and anaesthesiologists can work on when
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29 patients are booked for surgery.
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37 Of all the preoperative liver function and coagulation tests performed, high alanine
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39 transaminase/glutamic-pyruvic transaminases (ALT/GPT) concentration was the only
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41 independent biochemical risk factor associated with enhanced recovery failures. The
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43 strong association is indicative of the high risk of operating on an acutely inflamed
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45 liver.²⁸ A previous study²⁹ found that alanine aminotransferase ≥ 70 IU/L was an
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47 independent risk factor (odd ratio 2.02, 95% CI, 1.33 to 3.07) for postoperative
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49 complications after hepatic resection for hepatocellular carcinoma.
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54 Fast-track open liver resection was associated with a reduction in general
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56 complications as defined by the Postoperative Morbidity Survey¹⁷ by 36% (95% CI
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3 16% to 52%).¹⁹ A direct comparison between our incidence of postoperative
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5 morbidities on the third day after surgery and Jones et al.'s study¹⁹ is difficult as the
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7 timing of their postoperative morbidities was not specified. Our GEE model found
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9 that patients with any postoperative morbidity on the third day after surgery were
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11 three times more likely to be an enhanced recovery failure than patients without
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13 reported postoperative morbidity. Specifically, after adjustment for multiple testing,
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15 cardiovascular events (diagnostic tests or treatment in last 24 h for new myocardial
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17 infarction or ischaemia, hypotension, arrhythmias, cardiogenic pulmonary oedema or
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19 thrombotic events)¹⁷ was weakly associated with the risk of failure. **Early**
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21 **postoperative morbidities are associated with longer duration of hospital stay³⁰ and**
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23 **an increased risk of hospital readmission.³¹**
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30 Using a minimal important difference of 0.03,³² we found that patients in the
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32 enhanced recovery failure group had lower health-related quality of life than in the
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34 successful group. Our health-related quality of life on the third day after surgery in
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36 the successful group was similar to those reported in the standard care group by
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38 Jones et al.¹⁹ Our practice does not include carbohydrate drink up to 2 hours before
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40 surgery, pharmacological prophylaxis for deep vein thrombosis or the routine use of
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42 epidural anaesthesia.
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48 Overall, the results of this study suggest that it is possible to identify a subgroup of
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50 patients requiring additional care to minimize perioperative morbidity and length of
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52 stay. Patients who are smokers, have high ALT/GPT concentration or are at a high
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54 risk of postoperative morbidities are likely to fail enhanced recovery protocol in HBP
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56 surgery. In defining who is at high risk of postoperative morbidities, the American
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3 Society of Anesthesiologists' Physical Status grades III and IV and risk more than 50%
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5 estimated in the POSSUM-defined postoperative morbidity model may be useful as
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7 surrogate markers.¹⁷ For those patients at high risk of HBP surgery failure, elective
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9 postoperative ICU admission and measures targeted to avoid postoperative
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11 cardiorespiratory complications are warranted to reduce the risk of failure of
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13 enhanced recovery events.
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18 There are several limitations of this study. First, we did not measure the compliance
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20 rate of individual components of the ERAHBPS program. Recent studies suggest
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22 that better patient care and outcome can be achieved regardless of the number, the
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24 combination, the type, and the strength of evidence of the individual ERAS
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26 component.^{33;34} Second, the common-effects GEE analysis was influenced by the
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28 higher frequencies of prolonged ICU length of stay (12%) and hospital readmissions
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30 (6%) events than other components included in the definition of failure. Our sample
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32 size was small for the use an average relative-effect GEE analysis²⁰ to address this
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34 problem. There is a potential for residual confounding despite the use of multivariate
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36 analyses in this cohort study. The applicability of the identified risk factors to select
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38 patients suitable for ERAHBPS programs in other settings requires further validation.
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41 Finally, the failure outcomes were limited to the early to intermediate phases of
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43 recovery; we did not measure outpatient complications³¹ or late recovery outcomes,
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45 such as functional status and health-related quality of life beyond one month as
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47 recommended recently by Neville et al.³⁵
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54 In conclusion, patients who smoked, had elevated preoperative ALT/GPT or
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56 experienced postoperative morbidities were at risk of failing enhanced recovery
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3 protocols in major HBP surgery and may benefit from additional care. Patients who
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5 failed enhanced recovery protocols in HBP surgery stayed in ICU and in the hospital
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7 longer.
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10 11 **Acknowledgements**

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13
14 **Funding Support:** The work was substantially supported by the Health and Health
15
16 Services Research Fund, Food and Health Bureau, Hong Kong SAR Government
17
18 (Grant number: 08090311). The funding source had no role in the design, conduct or
19
20 analysis of the study, or in the decision to submit the manuscript for publication.
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23 **Competing Interests:** None declared.
24

25 **Ethics approval:** The Joint Chinese University of Hong Kong-New Territories East
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27 Cluster Clinical Research Ethics Committee approved this cohort study of patients
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29 undergoing major HBP surgery at the Prince of Wales Hospital in Hong Kong
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31 between January 2011 and November 2012 (CRE-2013.181).
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34 **Contributors:** AL performed the statistical analyses and had full access to all the
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36 data in the study. AL drafted the manuscript and made substantial revisions. All
37
38 authors were involved in the study concept and design of the study. CHC collected
39
40 the data. AL, MWAC, CDC, KFL, YSC and BSPL interpreted the data. All authors
41
42 made critical revisions of the manuscript for important intellectual content and
43
44 approved the final version of the manuscript. AL is guarantor.
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47 **Data sharing:** No additional data available
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49 **Provenance and peer review:** Not commissioned, externally peer reviewed.
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3 Figure 1. The incidence of postoperative morbidities on the third day after surgery by
4 enhanced recovery protocol groups. To control for type I error at 0.05 from multiple
5 comparisons, $P < 0.0063$ was considered significant
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