의학석사 학위논문

간담췌 정규 수술을 받은 후 예기치 않게 중환자실에 입실한 환자들의 불량한 예후에 영향을 미치는 위험인자

Risk factors of unfavorable outcome of patients who experienced unplanned ICU admission following elective Hepatobiliary & Pancreas surgery

울산대학교 대학원

의 학 과

손 지 민

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이 논문을 의학석사 학위 논문으로 제출함

2022 년 2 월

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국문요약

간담췌 수술은 술 후 합병증 발생률과 사망률이 높은 것으로 알려져 있다. 고위험 수술로 인하여 일부 환자들은 예기치 않게 중환자실 치료가 필요하며, 이 환자들의 상태나 예후를 예측하는 것은 임상적으로 중요하다. 최근에는 간담췌 수술 후 정례적인 중환자실 입실은 드물며, 합병증 발생 등으로 갑자기 중환자실 치료가 필요 경우가 대부분이다. 이 환자들의 특성을 파악하여 임상경과를 예측하고 치료하는 것은 매우 중요하다고 할 수 있다.

본 연구는 단일기관 후향적 연구로 2014년 1월 1일부터 2020년 12월 31일까지 7년간 서울아산병원 간담췌 외과에서 수술을 받은 23,041의 환자 중 응급수술, 간담췌 이외 질환의 동반 수술, 감시관찰만을 위한 입실, 수술 전부터 중환자실에서 치료 중이었던 환자를 제외하고, 간담췌 수술 후 합병증 발생으로 예기치 않게 중환자실에 입실한 165명의 환자를 대상으로 unfavorable outcome(사망 혹은 7일 이상의 중환자실 재원)에 영향을 미치는 인자들을 분석했다.

Favorable outcome을 보인 군(73명)과 unfavorable outcome을 보인 군(92명)으로 나누어 비교했을 때는 나이, Age-adjusted Charlson comorbidity index(ACCI) score, ASA PS(The American Society of Anesthesiologists physical status) classification, 간절제술 + 간외 담도절제술 혹은 간췌십이지장절제술, 수술일로부터 중환자실 입실일까지 소요일, 중환자실 입실 원인, APACHE IV score에서 양 군간 유의한 차이가 있었다. 이 중 다변량 로지스틱 회귀분석에서 unfavorable outcome을 유발하는 독립 인자는 간절제술 + 담도절제술 혹은 간췌십이지장절제술, 75점 이상의 APACHE(Acute Physiology and Chronic Health Evaluation) IV score, 패혈증으로 중환자실에 입실 한 경우 및 높은 ACCI score 였다.

결론적으로 간담췌 수술 후 예기치 않게 중환자실에 입실한 환자에서 많은 동반질환, 복잡한 간담췌 수술과 중환자실 입실 당시의 환자 상태의 심각성 및 패혈증을 동반한 합병증은 불량한 예후인자라고 할 수 있으므로 각별한 주의와 집중관찰 및 치료가 필요할 것으로 사료된다.

Abstract

Background: Hepatobiliary & pancreas (HBP) surgery is related to high rate of severe complication or perioperative mortality. Recently, fewer patients are admitted in the intensive care unit (ICU) routinely immediately after undergoing a major HBP surgery. Hence, it is necessary to have a comprehensive understanding of the patients who experienced unplanned ICU admission (UIA) due to severe postoperative complications. We aimed to identify the prognostic factors of these patients to predict their clinical course and to treat them accordingly.

Methods: This single-center retrospective cohort study was conducted in Seoul Asan Medical Center. We enrolled patients who required UIA following an HBP surgery from January 1, 2014 to December 31, 2020. Those who underwent emergency surgery, were co-operated in another department, were readmitted in the hospital, underwent routine ICU admission <48 h after surgery, and were admitted in the ICU before surgery were excluded.

Results: In total, 165 patients met the inclusion criteria, with a mean age of 66.6 years; of them, 76.4% were men. The mean age-adjusted Charlson comorbidity index (ACCI) score was 5.11, and the mean body mass index was 23.6 kg/m^2. Pancreaticoduodenectomy was the most common type of surgery (35.2%, 58/165). The mean duration of surgery was 304 min; the mean Acute Physiology and Chronic Health Evaluation (APACHE) IV score was 80.9. The mean length from index surgery to initial ICU admission was 6.9 days; the mean length of stay (LOS) in the ICU was 14.3 days; the mean length of hospital stay was 40.4 days; and the mortality rate was 29.1%. Compared with the favorable outcome group (n=73), the unfavorable outcome (mortality+LOS in ICU ≥7 days) group was older (age 69.6 vs 62.8 years, p<.001) and had a higher ACCI score (5.6 vs 4.5, p<.001). They had higher rates of obtaining an American Society of Anesthesiologists physical status score of 3 (35.6% vs 12.3%, p=0.038), undergoing hepatectomy + extrahepatic bile duct resection or hepatopancreatoduodenectomy (40.2% vs 19.2%, p=0.004), and developing sepsis as reasons for ICU admission (43.5% vs 17.8%, p=0.003). In addition, the index surgery to ICU admission was longer (8.7 vs 4.7, p=0.020) and the APACHE IV score was higher by 20 points (90.3 vs 69.8, p<.001). Among these, the higher ACCI score, surgery type, sepsis at UIA, and an APACHE IV score of >75 were independently significant prognostic factors.

Conclusion: For UIA patients following elective HBP surgery with higher ACCI score, complex operation type, severe condition (APACHE IV score > 75) or sepsis at UIA are likely to fall in unfavorable outcome, therefore, they should be monitored closely and treated accordingly.

Contents

List of tables and figures

Introduction

In previous studies, the indications for hepatic, biliary, and pancreatic (HBP) surgery were extremely limited owing to a high rates of mortality and severe morbidity and its challenging technical difficulties. However, with a significant improvement in the perioperative knowledge and in the HBP surgical technique over the past 3 decades, the total number of HBP procedures have markedly increased. (1-3) Intensive care unit (ICU) admission following HBP surgery is sometimes essential due to the complex nature of the surgery and the patients' preexisting co-morbidities. Especially, severe complications may lead to unplanned intensive care unit admission (UIA) and result in a poor outcome after HBP surgery.

With advancement in critical care, the outcomes of ICU patients have markedly improved. In an effort to identify the modifiable adverse factors that can lead to ICU admission or poor prognosis, a risk prediction system including the Acute Physiology and Chronic Health Evaluation (APACHE) score, Sequential Organ Failure Assessment (SOFA), and Quick SOFA was developed (4-6).

Several literatures have identified the risk factors for developing complications after a HBP surgery in general population, however, only a few researches performed a risk stratification of the patients who required UIA following HBP surgery. This retrospective study aimed to identify the risk factors of unfavorable outcomes and to establish the risk stratification for appropriate intensive care of patients who required UIA following an elective HBP surgery.

Methods

Patients

This is a retrospective study included a cohort of the patients who experienced UIA following HBP surgery at the Asan Medical Center, Seoul, South Korea from January 1, 2014 to December 31, 2020.

Patients with planned ICU admission for monitoring who underwent index operation as an emergency procedure or were co-operated in another department, who were admitted to the ICU before surgery or were readmitted in the hospital, and who did not undergo planned major resection due to peritoneal seeding were excluded.

Patient's data were obtained by reviewing the electronic medical records (EMRs) retrospectively. Age, sex, comorbidities, American Society of Anesthesiologists physical status (ASA PS) classification, surgery date, duration of surgery, type of operation, diagnosis requiring surgery, date of ICU admission and discharge, length of stay (LOS) of ICU, complications requiring UIA (which were subdivided into 4 categories: bleeding, sepsis, cardiopulmonary complications and others), body mass index (BMI) and lactic acid and C-reactive protein (CRP) levels at ICU admission were extracted. The study hospital had an EMR system where several data can be automatically extracted to calculate APACHE IV score within first 24 h; this score and every variable of this score system (age, temperature, mean arterial pressure, heart rate, respiration rate, whether mechanical ventilation was used, fraction of inspired oxygen, partial pressure of oxygen, partial pressure of carbon dioxide, arterial potential of hydrogen, serum sodium, 24-h urine output, creatinine, urea, serum glucose level, serum albumin, bilirubin, hematocrit, white blood cell count, Glasgow coma scale, comorbidities [chronic renal failure, lymphoma, liver cirrhosis, leukemia, hepatic failure, immunosuppression, metastatic carcinoma or acquired immunodeficiency syndrome], length of stay of previous ICU stay, origin of patient before admission to the ICU, whether it was readmission to ICU, whether it was following an emergency surgery, admission type, problem causing organ system, diagnosis, and whether thrombolysis was performed) were retrieved in the analysis. Before March 2019, the hospital used APACHE II score instead of the APACHE IV score; hence a common variable was used, and the chart to was reviewed to provide additional variables to re-calculate the APACHE IV score. Calculation was performed through the intrinsic calculation program of the EMR used in the hospital.

In the study hospital, most patients were not routinely admitted to ICU following a major HBP surgery due to the limited ICU resources. Only selected patients were immediately admitted to the ICU after surgery due to the severity of their condition or complex nature of surgery. Most of the patients stayed in the general ward after surgery unless an unexpected event occurred, which required ICU admission.

A medical alert team using an EMR-based screening system has been developed to manage patients with unexpected life-threatening complication. The approach used by the medical alert team to manage patients at risk of having an unstable status, such as those experiencing septic shock or hypovolemic shock with bleeding contributed to the early recognition of deterioration and early resuscitation.

The detection criteria in the EMR-based screening system established by medical alert team in our hospital are shown in table 1. The criteria included unstable vital sign, deterioration in the levels of biomarkers, and presentation of several clinical symptoms or situations.

The complications were divided into four groups, including bleeding, sepsis, cardiopulmonary complications, and others. Bleeding comprised early and late hemorrhage according to International Study Group of Pancreatic Surgery (ISGPS) and International Study Group of Liver Surgery (ISGLS). (7, 8) Sepsis was defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection according to the Third International Consensus Definitions for Sepsis and Septic shock, and the sources of sepsis were reviewed (9). Cardiopulmonary complications were divided into cardiologic and pulmonary complications. Pulmonary complications were classified according to the European joint taskforce perioperative clinical outcomes. (10) Cardiologic complications were defined according to the Standardized Endpoints in Perioperative Medicine and recorded. (11) This study was approved by the institutional review board of the Asan Medical Center, Seoul, South Korea (IRB approval number: 2021-1483)

Table 1. Detection criteria used in the electronic medical record screening system of our medical alert team

Unstable vital sign
Systolic BP < 85mmHg
Unexplained HR > 140 or <40 per min
RR > 28 or <8 per min
SpO2 ≤ 90%
Biomarkers
PaO2 < 55mmHg or PaCO2 > 50mmHg
PH < 7.3 or Lactic acid > 2mmol/L or TCO2 < 12mmol/L
Clinical examination and situation
Applying O2 > 9L or Venturi mask >35%
Sudden mental change or unexplained agitation
Bedside nurse concern about overall deterioration

Statistical analysis

An unfavorable outcome was defined as mortality or LOS in the ICU for ≥7 days. All data are expressed as number with percentages for categorical variables, mean with standard deviation for continuous. The difference between the unfavorable group and favorable group were analyzed using independent t test or a Mann Whitney U test for continuous variables and using Chi square statistics or Pearson's exact test for categorical variables. Multivariate binary logistic regression was performed to determine the independent predictors of unfavorable outcome among the clinically and statistically significant variables. Statistical calculations were performed using computerized statistical programs (SPSS 25.0, Chicago, IL, and GraphPad Prism 6, San Diego, CA, USA). P value < 0.05 was considered significant.

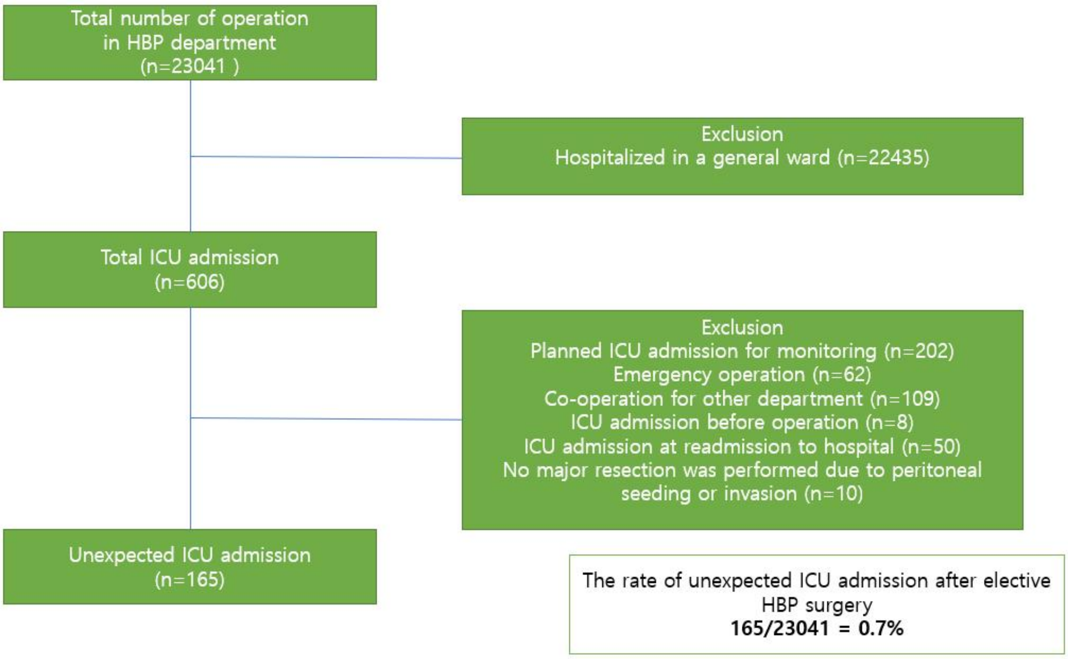
Results

Patient characteristics

Among the patients who underwent surgery at the HBP Surgery Department of Seoul Asan Medical Center from January 1, 2014 to December 31, 2020 (n=23,041), 606 experienced ICU admission (2.6%). Patients who experienced planned ICU admission within 48 h for monitoring (n=202), who did not undergo resection due to peritoneal seeding (n=10), who underwent index surgery as an emergency procedure (n=62), who were admitted in the ICU before surgery (n=8), whose surgery was performed as an cooperation to the surgeons from other departments (n=109), and who were readmitted to the ICU after discharge from the hospital (n=50) were excluded. The rate of UIA following elective HBP surgery was 0.7%.

The mean age of the subjects was 66.6 ± 10.1 years and 76.4% (n=126) were men. Five patients (3.0%) had an ASA PS class 1, while 125 (75.8%) and 35 (21.2%) had classes 2 and 3, respectively. The mean age-adjusted Charlson comorbidity index (ACCI) score was 5.11 ± 1.63.

Figure 1. Flowchart of the inclusion and exclusion of patients



Pancreatic mass was the leading diagnosis (n=46, 27.9%) requiring surgery, followed by hilar cholangiocarcinoma (CCC) (n=40, 24.2%). A total of 35 patients (21.2%) had distal CCC, while 12 (7.3%) had hepatocellular carcinoma (HCC). Nine patients had ampulla of Vater cancer (5.5%) , six had benign bile duct disease (3.6%), five had liver metastasis (3.0%), four had gallbladder cancer(2.4%), and three had intrahepatic CCC (1.8%), and five (3.0%) had other types of diseases.

Surgery type was classified into nine groups. Approximately 35.2% (n=58) of the patients underwent pancreaticoduodenectomy (PD), Thirteen underwent hepatopancreatoduodenectomy (HPD) (7.9%) , 38 underwent hepatectomy + extrahepatic bile duct resection (BDR) (23.0%), and 22 underwent hepatectomy (13.3%). A total of 83 patients underwent pancreatectomy; of them, 58 patients underwent PD (35.2%), 18 underwent distal pancreatectomy (10.9%), 4 underwent total pancreatectomy (2.4%), 3 underwent central pancreatectomy (1.8%). And 2 (1.2%) underwent other types of surgery

The total mortality rate in UIA patients was 29.1% (n=48). The reoperation rate was 47.3% (n=78), the mean duration from surgery to initial admission to ICU was 6.9 ± 10.2 days and the mean length of ICU stay was 14.3 ± 21.1. The mean length of total hospital stay of subjects were 40.4 ± 34.9. The mean BMI was 23.8 ± 3.6 kg/m^2 and the mean duration of surgery was 304 ± 112 min. The mean lactic acid and CRP levels were 4.4 ± 3.8 mmol/L and 8.4 ± 7.2 mg/dL respectively; meanwhile, the mean APACHE IV score was 80.9 ± 22.1.

Comparison between unfavorable group and favorable group (Table 2)

In this study, the patients were also divided into two groups; the unfavorable group, which included patients who died and with a length of ICU stay of > 7 days, and favorable group, which included patients with a length of ICU stay < 7 days. A total of 73 patients were included in the favorable group, while 92 were included in the unfavorable group. The sex distribution and BMI were not significantly different between the two groups. The duration of operation time and re-operation rate were not also significantly different. By contrast, the mean age of the unfavorable was older than that of favorable group's age (69.6 vs 62.8, p<.001). The mean ACCI score of the unfavorable group was 5.6, which was significantly higher than that of the favorable group (4.5) (P<0.001). The unfavorable group had higher proportions of patients with an ASA PS class 3, and this result was significant. The Favorable group tended to admit in ICU 4 days earlier than unfavorable group referring to the date of index operation. (4.7 vs 8.7, p=0.020). The unfavorable group had higher rates of hepatectomy + BDR/HPD (40.2% vs 19.2%, p=0.004) and malignancy (90.2% vs 72.6%, p=0.004). Moreover, this group had a significantly longer mean length of hospital stay (51.6 vs 26.3, p<.001), higher mean lactic acid and CRP levels, and a higher mean APACHE IV score (90.3 vs 69.8, p<.001).

Table 2. Baseline characteristics of the participants

Variables	Value (n = 165)
Age, mean ± SD (range), years	66.6 ± 10.1
SEX	
Male	126 (76.4%)
Female	39 (23.6%)
ASA PS	
1	5 (3.0%)
2	125 (75.8%)
3	35 (21.2%)
Age-Adujsted Charlson Comorbidity Index Score, mean ± SD (range)	5.11 ± 1.63
BMI, mean ± SD (range), kg/㎡	23.8 ± 3.6
Diagnosis	
Pancreatic mass	46 (27.9%)
Hilar CCC	40 (24.2%)
Distal CCC	35 (21.2%)
HCC	12 (7.3%)
AoV Cancer	9 (5.5%)
Benign Bile duct disease	6 (3.6%)
Liver metastasis	5 (3.0%)
Gallbladder cancer	4 (2.4%)
Intrahepatic CCC	3 (1.8%)
Others	5 (3.0%)
Operation	
Hepatopancreatoduodenectomy	13 (7.9%)
Hepatectomy + Bile duct resection	38 (23.0%)
Hepatectomy	22 (13.3%)
Bile duct resection	7 (4.2%)
Pancreaticoduodenectomy	58 (35.2%)
Distal pancreatectomy	18 (10.9%)
Total pancreatectomy	4 (2.4%)
Central pancreatectomy	3 (1.8%)
Others	2 (1.2%)
Initial Reason for ICU admission	
Bleeding	54 (32.7%)
Sepsis	53 (32.1%)
Cardiopulmonary problems	38 (23.1%)
Others	20 (12.1%)
Reoperation	78 (47.3%)
Length from index surgery to initial admission to ICU, mean ± SD (range), days	6.9 ± 10.2
Length of ICU stay, mean ± SD (range), days	14.3 ± 21.1

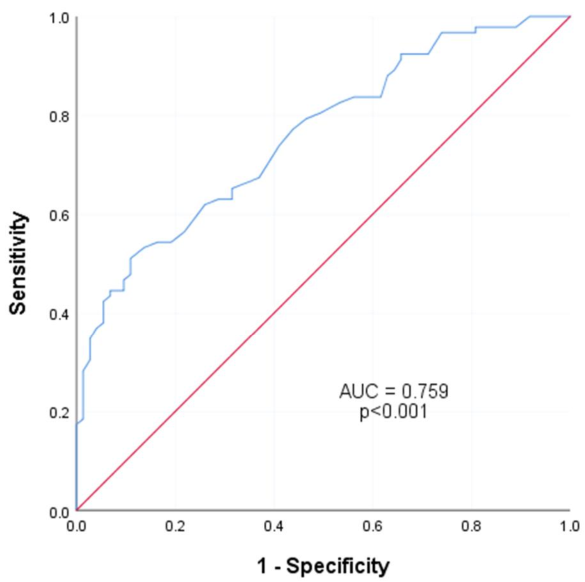
Length of total hospital stay, mean ± SD (range), days	40.4 ± 34.9
Mortality	48 (29.1%)
Duration of Operation, mean ± SD (range), min	304 ± 112
Lactic acid, mean ± SD (range), mmol/L	4.4 ± 3.8
CRP, mean ± SD (range), mg/dL	8.4 ± 7.2
APACHE IV score, mean ± SD (range)	80.9 ± 22.1

SD; standard deviation, ASA PS; American Society of Anesthesiologists performance status, BMI; body mass index, CCC; Cholangiocarcinoma, AoV; ampulla of Vater, ICU; Intensive care unit, APACHE; Acute Physiology and Chronic Health Evaluation, CRP; C-reactive protein

Receiver operating characteristic (ROC) & Cut-off value of APACHE IV score (Figure 2)

APACHE IV was evaluated using the area under curve (AUC) of the receiver operating characteristic curve as a measure of discrimination of unfavorable outcome in this study. The AUC was 0.759 with a p value of < .001. The cut-off value was 75.5

Figure 2. Receiver operating characteristic curves of unfavorable outcome prediction based on the Acute Physiology and Chronic Health Evaluation IV scores



AUC : Area under curve

Table 3. Univariate analysis of mortality/longer ICU stay of patients who required unplanned ICU admission

	Favorable group (n=73)	Unfavorable group (n=92)	*P*-value
Sex			
M	56 (76.7%)	70 (76.1%)	
F	17 (23.3%)	22 (23.9%)	0.925
Age, mean ± SD (range), years	62.8 ± 9.8	69.6± 9.3	<.001
Age- adjusted Charlson comorbidity index score, mean ± SD (range)	4.5±1.6	5.6±1.5	<.001
ASA PS			0.025
1	4 (5.5%)	1 (1.1%)	
2	60 (82.2%)	65 (70.7%)	0.195
3	9 (12.3%)	26 (35.6%)	0.038
BMI, mean ± SD (range), kg/㎡	23.6±3.0	24.0±3.9	0.488
Diagnosis			
Benign	20 (27.4%)	9 (9.8%)	0.004
Malignancy	53 (72.6%)	83 (90.2%)	
Operation			
Hepatectomy + BDR / HPD	14 (19.2%)	37 (40.2%)	0.004
Duration of Operation time, mean ± SD (range), min	294 ± 92	312 ± 124	0.304
Length of day from index operation to ICU admission, mean ± SD (range), days	4.7 ± 5.3	8.7± 12.6	0.020
Reason for ICU admission			0.003
Sepsis	13 (17.8%)	40 (43.5%)	
Bleeding	33 (45.2%)	21 (22.8%)	<.001
Cardiopulmonary	17 (23.3%)	21 (22.8%)	0.046
Others	10 (13.7%)	10 (10.9%)	0.041
Re operation	32 (43.8%)	46 (50%)	0.431
Length of total hospital stay, mean ± SD (range), days	26.3± 15.4	51.6 ± 41.4	<.001
Lactic acid, mean ± SD (range), mmol/L	3.9± 3.6	4.9± 3.9	0.089
CRP, mean ± SD (range), mg/dL	7.4± 6.7	9.2± 7.6	0.113
APACHE IV score, mean ± SD (range)	69.8± 15.1	90.3± 22.9	<.001

ICU; Intensive care unit, SD; Standard deviation, ASA PS; American Society of Anesthesiologists performance status, BMI; body mass index, BDR; Bile duct resection, HPD; Hepatopancreatoduodenectomy, ICU; Intensive care unit, APACHE; Acute Physiology and Chronic Health Evaluation, CRP; C-reactive protein

Table 4. Classification of complications

Complication	N
Bleeding	**54**
Early bleeding	***32***
Liver cut surface	7
Pancreas cut surface	8
Mesocolon	3
RHA br.	2
Rt Inferior Phrenic artery br.	2
SMA br.	2
Splenic artery	1
RGA	1
RGEA	1
MHA	1
MHV	1
GDA	1
Adrenal gland	1
Intraoperative massive bleeding	1
Late bleeding	***22***
Pseudoaneurysm	17
Failure of hemostasis	4
Luminal bleeding	1
Sepsis	**53**
Surgical Site Infection	
Organ	20
Deep	1
POPF	10
Cholangitis	7
Bowel Perforation	7
Bile leakage	5
Bowel ischemia	1
Bowel obstruction	1
Pseudomembranous colitis	1
Cardiopulmonary	**38**
Cardiologic	***12***
Myocardial infarction	5
New cardiac arrhythmia	6
Deep vein thrombosis	1
Pulmonary	***26***
Respiratory failure	9
Aspiration pneumonitis	7
Pneumonia	2
Atelectasis	2
Pleural effusion	2
ARDS	1

Pneumothorax	1
Pulmonary edema	1
Pulmonary embolism	1
Others	**20**
Acute Liver injury	10
Renal complication	3
Neurologic complication	6
Adrenal insufficiency	1

RHA; Right hepatic artery, br.; branch, Rt; Right, SMA; Superior mesenteric artery, RGA; Right gastric artery, RGEA; Right gastroepiploic artery, MHA; Middle hepatic artery, MHV; Middle hepatic vein, GDA; Gastroduodenal artery, POPF; Postoperative pancreatic fistula, ARDS; Acute respiratory distress syndrome

Table 5. Multivariate analysis of mortality/longer ICU stay of patients who required unplanned ICU admission

	Odd ratio (95 % C.I)	*P*-value
Age-adjusted Charlson comorbidity index score	1.44(1.07~1.94)	0.015
ASA PS		0.539
1	Ref	
2	0.44(0.04~5.44)	0.525
3	0.71(0.47~10.72)	0.806
Diagnosis		0.136
Benign	Ref	
Malignancy	2.39(0.76~7.50)	
Operation		
Hepatectomy + BDR / HPD	3.65(1.49~8.87)	0.005
Length of day from index operation to ICU admission	1.06(0.99~1.13)	0.081
Reason for ICU admission		0.010
Sepsis	Ref	
Bleeding	0.19 (0.07~0.53)	0.001
Cardiopulmonary	0.41 (0.14~1.21)	0.106
Others	0.21 (0.06~0.77)	0.019
APACHE IV score >75	3.29(1.48~7.31)	0.003

C.I; Confidence interval, ASA PS; The American Society of Anesthesiologists physical status, BDR; bile duct resection, HPD; Hepatopancreatoduodenectomy, ICU; Intensive care unit, APACHE; Acute Physiology and Chronic Health Evaluation

Classifications of complications (Table 4)

In 165 patients, bleeding was the most frequent complication followed by sepsis. Among 54 patients who experienced bleeding, 32 had bleeding within 24 h after surgery and 22 had late hemorrhage. The pancreatic cut surface and liver cut surface were the two most common location of early bleeding. Three of the patients had early bleeding in the mesocolon. Of the 22 patients who had late bleeding, 17 had pseudoaneurysm ruptures, 3 had bleeding caused by failure to achieve hemostasis, and 1 had luminal bleeding.

Fifty-three patients experienced bleeding due to sepsis. The most common cause of sepsis was organ/space surgical site infection (20 cases), followed by postoperative pancreatic fistula (10 cases). Cholangitis and bowel perforation were the primary causes of sepsis in each seven patients, while bile leakage was the primary cause of sepsis in five. A total of 38 patients developed cardiopulmonary complications, of whom 12 had cardiologic complications and 26 pulmonary complications. Among the 12 patients who developed cardiologic complications, 5 had myocardial infarction, 6 had new cardiac arrhythmia and 1 deep vein thrombosis. Of the 26 patients with pulmonary complications, 9 (34.6%) had respiratory failure, while 7 (26.9%) had aspiration pneumonitis. Among others category, acute liver injury was the most common cause (10/20, 50%), followed by neurologic complication. (6/20, 30%)

Multivariate analysis (Table 5)

Except for the length of total hospital stay which often works as an outcome rather than independent variable, the factors with statistical significance were included in the multivariate analysis. The ACCI was an independent risk factor of unfavorable outcome (odds ratio [OR]: 1.44, p=0.015), while surgery type (hepatectomy with extrahepatic BDR or HPD) was a risk factor with significance (OR: 3.65, p=0.005). Patients admitted in the ICU due to sepsis (p=0.010) or with an APACHE IV score >75 was at a higher risk of unfavorable outcomes (OR 3.29, p=0.003). ASA PS class, malignancy and length of day from index surgery to ICU admission were not considered as an independent factor in the multivariable analysis.

Discussion

HBP surgery carries a significant risk of morbidity and mortality due to the complex nature of the surgery and the patients' preexisting co-morbidities. Although several single-center studies have reported a reduction in the risk of HBP surgery over time, it is still associated with considerable risks of severe complication and mortality; hence, patients who undergo HBP surgery often require ICU care, which invariably uses major hospital resources, is highly expensive and is often associated with worst outcomes

Among patients requiring ICU admission, those experiencing UIA should be discussed separately; this is because this group of patients has worse outcomes compared with the group of patients who underwent planned admission group. (12, 13) In the current study, among the patients who underwent HBP surgery within the 7- year period, 2.6% were admitted to the ICU, while 0.7% experienced UIA. The rate of unfavorable outcome, which comprised in-hospital mortality or ICU stay for ≥ 7 days, was 55.8%, which was relatively high as expected. Four factors including a higher ACCI score, hepatectomy combined with extrahepatic bile duct resection, sepsis at ICU admission, and an APACHE IV score >75 were the independent risk factors of unfavorable outcome. This was the first study to evaluate the risk factors of unfavorable outcomes among patients with UIA following HBP surgery. Hence, the patients should be stratified according to the severity of morbidity and their clinical course should be accurately predicted; moreover, appropriate intensive care should be provided in patients who required UIA.

In previous studies reporting the morbidity and mortality rates following HBP surgery of 13,558 patients from the US, the perioperative outcomes depended on the surgery type, showing that extended hepatectomy was a risk factor of mortality and severe complication. (14) Compared with simple hepatectomy without extrahepatic bile duct resection, major hepatectomy with extrahepatic bile duct resection is largely different technique because it involves the performance of major hepatectomy with choledochojejunostomy using a Roux-en-Y method which disrupts the natural physiology of the biliary and gastrointestinal system. (15) The incidence of post-hepatectomy liver failure was considerably higher in the hepatectomy with an extrahepatic BDR group, and the percentage of regenerated liver volume after the hepatectomy on postoperative days 6-8 was significantly lower in the same group compared with that in the hepatectomies without extrahepatic BDR group according to the single-center retrospective study conducted in 2017. (16) Furthermore, it showed a difference in the morbidity rate, mortality rate, duration of operation time and volume of intraoperative blood loss, and argued the necessity of classification of these 2 operations. Patients requiring major hepatectomy with an extrahepatic BDR usually have a major biliary ductal obstruction at diagnosis. Hence, biliary drainage using a stent is often required preoperatively. Although this procedure is performed to improve the symptoms associated with obstructive jaundice, foreign material in biliary system causes contamination of the system. (17) Following the performance of BDR in the middle of operation, contaminated bile may infect the surgical field and it may lead to various degree of infections. (18) The creation of a choledochojejunostomy, which inevitably disrupts the system preventing regurgitation of bowel contents to the biliary system, may increase the risk of recurrent cholangitis following the surgery and lead to poor prognosis. Basic research conducted by the same institution demonstrated some of mechanisms of poor liver regeneration in a rat model with a major hepatectomy and choledochojejunostomy. In a rat model, the choledochojejunostomy induced the occurrence of cholangitis in the periportal area following the procedure and suppression of the expression of liver regeneration-associated factors. (19) These may explain the reduced hepatic regeneration rate in the former group. Therefore, those who underwent hepatectomy with extrahepatic BDR were classified as a separate group; this procedure still may act as an independent factor causing severe complications and lead to poor prognosis due to distinct features explained above.

In current study, the complications were divided into four categories: bleeding, sepsis, cardiopulmonary complications and others; sepsis at admission was a risk factor of unfavorable outcomes, and the bleeding group had highest rate of favorable outcomes. Among the 53 patients who required UIA due to bleeding, 32 (60.4%) were admitted in the ICU due to early active bleeding, which wars defined by International Study Groups of Pancreas Surgery, meaning direct failure of intraoperative hemostasis and coagulopathy. (8) As a previous study demonstrated, the outcome of early bleeding could be significantly improved if the diagnosis and management are performed within 6 h. (20) In our study, the early detection and intervention (re-operation or embolization) succeeded in rescuing patients without excessive prolongation of ICU care. More than half of cases (17/32, 53.1%) with early bleeding were transferred to the general ward within 48 h after admission (21).

After dividing the complications of UIA at admission into several categories, we found that most of cardiopulmonary complications had isolated single organ problems without abdominal infection, including respiratory failure, aspiration pneumonitis, acute myocardial infarction or newly developed arrhythmia. For example, patients admitted in the ICU due to sepsis who developed hospital-acquired pneumonia were included in the sepsis group. Therefore, the cardiopulmonary complications were considered as a single event rather than multiple serial events. The favorable outcomes of patients with postoperative cardiopulmonary complications, which were recognized as poor prognostic factors, may be due to the different classification system used in this study. (21)

In contrast, sepsis, which was a distinct and complex diagnosis, was defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. (9) Although the rate of inpatient mortality due to surgery-related sepsis has substantially decreased over the past 2 decades owing to Surviving Sepsis Campaign, it still remains one of the major challenges both in critical care and complex major surgery.(22, 23) Due to the initial intense inflammatory response, patients with sepsis may present with fever, shock, altered mental status, and organ dysfunction at an early phase. (24) Then, they may experience prolonged inflammation, immunosuppression and catabolism with elevated circulating pro inflammatory biomarkers and innate immune suppression up to 4 weeks after sepsis onset. The immune suppression associated with sepsis contributes to the late sepsis mortality in ICU patients due to the occurrence of secondary infections. (25) In a previous prospective ICU observational study, patients with sepsis at ICU admission repeatedly developed hospital acquired infection compared with those without sepsis at admission. (26) The sepsis group was more likely to have multiple and serial events rather than an isolated single event compared with the other group, thus frequently leading to multi-organ failure. The occurrence of sepsis at ICU admission led to unfavorable outcome in 75.5% (40/53) of patients; this finding is in accordance with those of previous reports, which demonstrated that sepsis at ICU admission was correlated with a higher rate of mortality and longer length of ICU stay compared with the absence of sepsis.(27, 28)

Due to the poor prognosis of sepsis, the prediction of mortality in patients with sepsis continues to be the main focus of critical care medicine. The accurate clinical risk prediction models can objectively estimate the disease severity and stratify patients according to the degree of mortality risk. They may be used to alert clinicians and to allow for the timely identification of high-risk populations that require aggressive management and intervention. Several predictive systems have been developed to date, including the APACHE II and IV scores, Sequential Organ Failure Assessment (SOFA) score and ACCI score.

The patient's score in the APACHE II tool developed by Knaus et al., a well-studied ubiquitous score that includes items related to chronic health factors and acute physiological derangements (taken within the first 24 h in the ICU), was a proven predictor of adverse outcomes in analysis of patients undergoing pancreatectomy, liver resection and liver transplantation. (29) The score thus underlines the role of early organ failure in the ultimate outcome of patients. The score may also be useful in predicting patients with a high risk of death or long ICU stay or ICU readmission. This may facilitate the appropriate treatment, triage and disposition of patients from the ICU. The APACHE II was updated to a more accurate version, the APACHE IV, after a series of improvements. Due to its time-consuming job of addressing many data (37 minutes per person), APACHE II and IV are being used concomitantly.

In this study, we used the APACHE IV score which was available for every patient, and it was proved to be a fairly good predictor of an unfavorable outcome in patients who required UIA following HBP surgery (AUC 0.758, $p<0.001$, cut-off value 75.5). The mean difference of APACHE IV score between unfavorable group and favorable group in current study was >20 points, with significance. (90.3 vs 69.8, $p<.001$) The severity at the time of ICU admission directly affects the outcome of the postoperative UIA group. The APACHE IV tool includes objective physiological factors, it largely eliminates the possibility of errors made by the user, and it is widely applicable because it can determine the patient's current clinical condition. Among UIA patients who developed severe postoperative event, a higher APACHE score may indicate the severity of current status and inability to detect the deterioration of patient's condition. The APACHE tool has some limitations: it cannot be used during UIA and requires a special calculation tool. However, since the lactic acid or CRP levels, which were more easily accessible, were not significant indicators, the APACHE score was the best predictor at the moment.

Age and patient's comorbidity were also reported to be poor prognostic factors of the outcomes of HBP surgery.(14) In this study, the ACCI was used to evaluate the prognostic factors of UIA.

In HBP surgery, Dias santos et al, demonstrated that ACCI of ≥6 was the strongest predictor of 1-year mortality following pancreatectomy, which nearly tripled the odds of death within the first year. (30) In addition, an ACCI score of > 6 showed greater risk of developing pleural effusion, pneumonia and surgical site infection following hepatectomy. (31) The ACCI is a statistically validated tool that assigns different weights to patients' comorbidities to predict mortality and can be adjusted for patient's age. It has been used extensively in studies on cancer and other medical conditions to predict the outcome and it can be applied in a more extended field.

As discussed earlier, postoperative UIA is strongly correlated with negative outcome. However, in a different perspective, UIA is more preferrable in patients who would benefit from ICU care but only if they will be treated only if patients will be treated appropriately without in order to achieve full recovery.

Although not shown in the result, 25% of patients with unfavorable outcomes experienced ICU readmission; this may indicate failure in assessment of the patient's exact clinical condition at ICU discharge. As this study suggested the risk factors of unfavorable outcomes in the UIA group, clinicians, including intensivisits, may consider these factors when planning to discharge the patients from the ICU.

Our study has some limitations. First, owing to the inherent bias in a single center retrospective study, further research is warranted to validate our findings. Second, due to the heterogeneity of surgery type and its postoperative courses, the analysis of these cases may lead to ambiguity, which can be better understood by conducting a sub-analysis in future study.

In the future, constructing a normogram using the significant variables identified in this study for prediction would be helpful in the clinical situation. Consistent effort in investigating the complication and perioperative morbidity of HBP surgery may enhance the understanding of the characteristics of these patients.

Conclusion

Despite recent improvement in HBP surgery and critical care field, some of patients who undergo HBP operation still experience UIA due to severe complications. In the current study, a higher ACCI, major hepatectomy combined with extrahepatic BDR, sepsis at the time of UIA and APACHE IV score > 75 were the risk factors of unfavorable outcomes. Both HBP surgeons and intensivists should consider these factors to predict patient's clinical course and provide intensive treatment.

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