Clinical effect of altitude level on surgical outcomes of pancreaticoduodenectomy for periampullary tumor: a multicenter study

Mohamed Attia[a], Mohamed El Sorogy[a], Hosam Hamed[a], Mahmoud Ali[a], El Sayed A. El Magd[a], Ayman El Nakeeb[a], Taha Kayed[b], Alaa M. Sewefy[b], Ahmad AlMalki[c], Ahmed Alqarni[c], Yousef Alhamada[c], Mohammed M. Mohammed[b]

[a]Gastroenterology Surgical Center, Mansoura University, [b]Gastroenterology Surgical Center, Minia University Hospital, Mansoura, Egypt, [c]Gastroenterology Surgical Center, Aseer Central Hospital, Aseer Region, Kingdom of Saudi Arabia

Correspondence to Mohamed Attia, MD, Gastroenterology Surgical Center, Mansoura University, Mansoura, 35516, Egypt. Tel: +20 100 842 0576; e-mail: dr_mohamedattia410@hotmail.com

Received: 31 March 2021
Revised: 18 April 2021
Accepted: 27 April 2021
Published: 11 January 2022

The Egyptian Journal of Surgery 2021, 40:842–849

Background
The data on the effect of altitude on surgical outcomes after pancreaticoduodenectomy (PD) are lacking. This research is designed to determine the surgical outcomes of PD for periampullary tumor in high altitudes compared with normal altitudes.
Patients and methods
This is a multicenter propensity score-matched study. At the normal-altitude region, 90 patients had PD and 45 patients had PD in high-altitude region. The primary outcome was postoperative complications development. Secondary outcomes included operating time, blood loss intraoperative, postoperative complications, mortality, hospital stay, and postoperative pathology.
Results
There were insignificant differences in tumor size, site and nature, safety margin, number of lymph node dissected, perivascular infiltration, and perineural infiltration between the two groups. There were no significant differences in hospital stay, time to oral ingestion, and overall complications between the two groups. The primary delayed gastric emptying, deep venous thrombosis (DVT), and pulmonary embolism (PE) were significantly higher at high altitude. Hospital mortality at high altitude was higher (*P*=0.07), with the main cause being PE in high-altitude area.
Conclusion
Primary delayed gastric emptying is a high-altitude complication following PD. High altitude was related to a high incidence of venous thromboembolism. Hospital mortality at high altitude was higher, and PE was the principal cause. Extended postoperative therapy with low-molecular-weight heparin is recommended for 28 days to decrease the occurrence of PE and mortality.

Keywords:
altitude level, delayed gastric emptying, pancreaticoduodenectomy, periampullary tumor, POPF, pulmonary embolism

Egyptian J Surgery 40:842–849

1110-1121

Introduction

Pancreaticoduodenectomy (PD) is the procedure of choice for a variety of malignant and benign periampullary diseases. It is a complex technique involving comprehensive dissection and three reconstructions. The result of PD has recently improved because of developments in surgical procedures, anesthesia, and perioperative treatment [1–4]. Although the findings from high-volume hospitals showed a decrease in hospital mortality to less than 3%, the rate of postoperative morbidity remains high, ranging from 20% to 60% [4–8].

The high-altitude climate includes a series of circumstances with low air pressure, hypoxia, and more ultraviolet emissions that are maybe intermingled with genes and other environmental elements in a compound system. The altitude level is graded as high altitude: 1500–2500 m; very high altitude: 2500–3500 m; and extremely high altitude: greater than 3500 m. Abha is the district capital of Aseer in Saudi Arabia. It is situated in the fertile Aseer Mountains of South-Western Saudi Arabia 2270 meters above sea level. It is a region of great altitude [9,10]. It is clear that some of the related altitude conditions can have specific effects on the risk factors of many diseases, such as pulmonary

DOI: 10.4103/ejs.ejs_109_21

hypertension and polycythemia, and associated mortality or life probability [9–11].

Many recent studies have suggested multiple risk factors affecting postoperative surgical outcomes of PD, including age, sex, obesity, liver cirrhosis, preoperative biliary drainage, pancreatic stump characteristics, method of pancreatic reconstruction, surgical technique, minimally invasive procedures, use of postoperative octreotide, and postoperative pathology [12–15].

Very few papers have examined the effect of living at high altitudes on surgical results of major operations. This research was designed to determine the effect of altitude level on surgical outcomes of PD for periampullary tumor.

Patients and methods

Patients and characteristics

Study design

This is a multicenter study of a likelihood score-matched examination for patients in high-altitude and normal-altitude regions experiencing PD of periampullary tumor. The data of consecutive patients who underwent PD for periampullary tumor included in the Gastrointestinal Surgical Center (Mansoura University), Menia University Hospital Egypt, and Aseer Central Hospital, Aseer Region, KAS, from March 2018 to April 2020, were included in the study. The criterion for inclusion included patients with either benign or malignant periampullary tumor diagnosed with mass or obstructive jaundice. Exclusion criteria included PD in cirrhotic, PD with vascular resection, locally advanced periampullary tumor, patients who underwent laparoscopic PD, and patients with a reconstruction of PD with pancreaticogastrostomy.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

The data were prospectively registered into a computerized archive. Consent form was signed by all patients to be included in this analysis, after thorough consideration of the characteristic of the periampullary tumor and also potential treatment options with its complications. IRB approved the analysis in all centers. This study is registered in ClinicalTrials.gov ID NCT04401722.

The patients were distributed into two groups: group I (G1) underwent PD in the area at the level of the sea, normal-altitude region, and group II (G2) underwent PD in high-altitude region.

Preoperative data

Preoperative assessment for the diagnosis and staging of periampullary tumor involved presentation, physical examination, liver function, full blood count, tumor markers, and imaging [abdominal ultrasound-magnetic resonance cholangiopancreatography, abdominal computed tomography (CT), and CT angiography]. Preoperative endoscopic biliary drainage was performed in cases presented with borderline tumor managed by neoadjuvant chemotherapy, cholangitis, or hepatic dysfunction as detailed in earlier publications [1,6].

Surgical procedures

For all cases, subtotal gastrectomy was performed with a classical PD. Pancreatic reconstruction was performed to the jejunum by pancreaticojejunostomy. Bilioenteric anastomosis (HJ) was done in the retrocolic fashion, in an end-to-side approach. Using vicryl or PDS sutures 4/0, HJ was performed in either interrupted, continuous, or combined manner. Gastrojejunostomy antecolic was performed side to side using a gastrointestinal tract stapler.

Postoperative management

Postoperative ICU stay was for 1 day for all patients, who were then transferred the next day to the general ward. Prophylactic antibiotic was administered intraoperatively and proceeded postoperatively for 5 days. Postoperatively, prophylactic octreotide was administered subcutaneously for 3 days, especially for patients at risk.

Regular documentation was provided of vital signs, intravenous fluid, and drain outputs. If intestinal sounds are heard, patients were able to begin fluid intake orally. When oral intake was tolerated, patients were discharged without any complications, and thereafter, the drains were removed.

Follow-up

Follow-up was scheduled postoperatively at 1 week, 1 month, 3 months, and 6 months, and then at 1 year. Follow-up included clinical evaluation; laboratory functions, such as complete blood count, liver function, exocrine, and endocrine pancreatic function; tumor marker (CEA and CA19-9); and abdominal CT to determine any complication and recurrence risk.

Definitions

The International Pancreatic Fistula Study Group described POPF, delayed gastric emptying (DGE), and biliary leakage [8]. Postoperative morbidities have been classified by Dindo *et al.* [16]. Postoperative mortality within 30 days of operation was described as hospital mortality.

Data collection

The database contained the following variable: demographic data, previous abdominal surgery, symptom length, BMI, comorbidity laboratory finding, radiological finding, surgical date, operational information, complications within 30 first postoperative days, and length of hospital stays (LOS).

Primary outcome

The primary outcome was the overall postoperative complications.

Secondary outcomes

The secondary outcomes are operative times, blood loss, blood transfusion, pancreatic stump criteria including texture and pancreatic duct diameter, technical difficulties, type of pancreatic reconstruction, cost, hospital stay, mortality rate, mass size, number of lymph node dissected, and postoperative pathology.

Statistical analysis

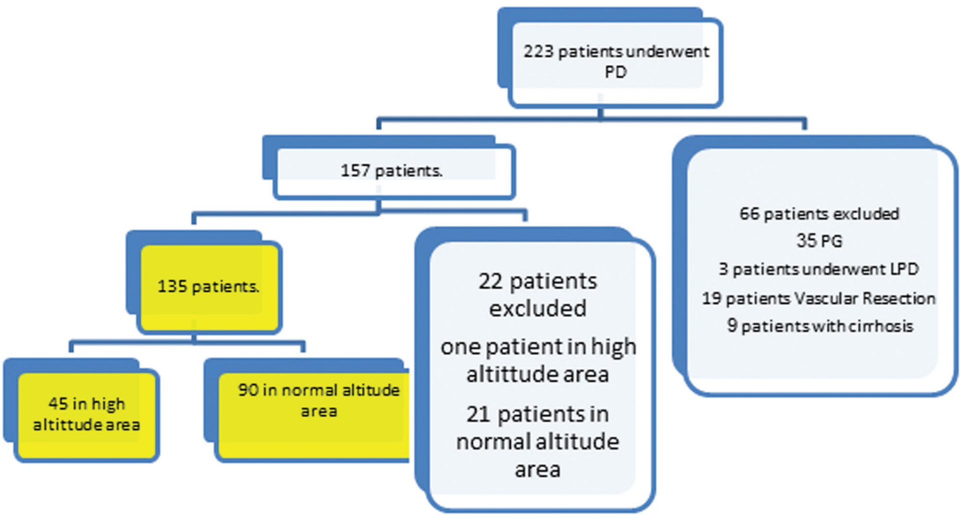
For categorical variables, descriptive data were expressed as counts and percentages. Continuous variables were described as a median. All statistical analyses were performed in Windows using SPSS 17 (SPSS Inc., Chicago, Illinois, USA).

Comparison of two classes of categorical variables was done by χ^2, and Student's *t*-testing was used for the continuous variables. A significant value is P less than 0.05. In multivariate logistic regression, preoperative data including demographic data, clinical presentation, comorbidity, and preoperative endoscopic retrograde cholangiopancreatography (ERCP) were entered to make propensity scores modeling the probability of a high-altitude, normal-altitude patient undergoing PD. A score-matched study of propensity was conducted to build matched groups using the nearest neighboring technique with match 1 : 2 and no caliper for optimal similarity.

Results

In the research period, 223 patients had PD, and 66 patients were excluded from the research [35 patients (PG), three patients had laparoscopic PD, 19 patients had vascular resection, and nine patients had cirrhosis of the liver]. A total of 157 patients entered a propensity score-matched examination, and only 135 patients participated in the sample, including 45 who had PD at high altitude, and 90 patients who had PD at a normal altitude (excluding one patient who had PD at high altitude and 21 patients who had PD at low altitude) (Fig. 1).

Figure 1



Flow chart for patients who underwent pancreaticoduodenectomy in the period between March 2018 and April 2020 (a propensity score-matched study).

Baseline characteristics

As for the preoperative results, both groups were well matched. Preoperative data are shown in Table 1.

Operative characteristics

Table 2 summarizes data from both groups intraoperatively. There were no major variations between the two groups aside from the diameter of the pancreatic duct, the blood loss, and the operating length. The median blood loss was 550 ml (100–1500) in group I and 800 ml (250–3000) in group II. The median total operating time in group II was significantly shorter in normal altitude [5 (3–7) vs. 5.5 (4–8) h] (*P*=0.004).

Postoperative course

There were insignificant differences between the two groups regarding postoperative stay, time to oral intake, and the time of drain removal. The distribution of postoperative complications is shown in Table 3.

There were no significant differences between the two groups with respect to complications rate and severity. There was no significant difference in the POPF rate and grade between both groups. At high altitude, the primary DGE, pulmonary complications, deep venous thrombosis (DVT), and pulmonary embolism (PE) were substantially higher. Wound infection is higher in high altitude but not reaching the significant value.

Hospital mortality was higher in high altitude [3 (3.3% vs. 5 (11.1%), *P*=0.07]. The main cause of hospital mortality was PE in high altitude region.

Histopathological results

There were insignificant differences in tumor size, site and nature, safety margin, number of lymph node dissected, perivascular infiltration, and perineural infiltration between the two groups (Table 4).

Discussion

PD is the standard treatment for periampullary resectable tumors [1–3]. PD is a complicated technique requiring thorough dissection and three anastomosis procedures. Owing to advances in surgical precision, anesthesia, and perioperative treatment, PD's postoperative outcomes have been settled [3–5]. Although hospital mortality declines after PD in specialized high-volume centers to less than 3%, the frequency of postoperative complications continues high, ranging from 40 to 60%. Postoperative morbidity leads to an extended hospital stay, rising costs, and death. Moreover, at specialized pancreatic

Table 1 Demographic data

Variables	PD in normal altitude [*n* (%)]	PD in high altitude [*n* (%)]	*P* values
Median age (years)	59 (28–70)	61.5 (44–81)	0.09
<60	33 (36.7)	19 (42.2)	0.53
>60	57 (63.3)	26 (57.8)	
Sex			
Male	63 (70)	28 (62.2)	0.36
Female	27 (30)	17 (37.8)	
BMI	29 (20–39)	28 (22–39)	0.86
<25	27 (30)	16 (35.6)	0.51
>25	63 (70)	29 (64.4)	
Symptoms			
Jaundice	68 (75.6)	33 (73.3)	0.78
Abdominal pain	57 (63.3)	26 (57.8)	0.53
Diabetes	31 (34.3)	15 (33.3)	0.89
Hypertension	22 (24.4)	13 (28.9)	0.62
Median preoperative Hg (g/dl)	11 (9–16)	11.6 (9.2–17)	0.2
Median preoperative albumin (g%)	3.7 (3–5)	3.5 (3–4.7)	0.25
Median preoperative bilirubin (mg%)	5.1 (0.6–20)	5.1 (1.1–23.5)	0.58
Median blood sugar (mg%)	120.5 (80–220)	107 (80–230)	0.21
Preoperative billiary drainage (ERCP)	54 (60)	29 (64.4)	0.62
Median preoperative CEA (ng/m)	43 (0.7–312)	50.5 (1–102)	0.79
<5	32 (35.6)	16 (35.6)	1
>5	58 (64.4)	29 (64.4)	
Median preoperative CA19-9 (U/ml)	155.5 (2–1200)	223 (25–1432)	0.34
<37	19 (21.1)	10 (22.2)	0.86
>37	71 (789)	35 (77.8)	

ERCP, endoscopic retrograde cholangiopancreatography; Hg, hemoglobin; PD, pancreaticoduodenectomy.

Table 2 Operative data

Variables	PD in normal altitude	PD in high altitude	*P* values
Tumor size (cm)			
Median tumor size (cm)	2 (1–5)	3 (1–5)	0.06
≤2 cm	68 (75.6)	40 (88.9)	0.07
>2 cm	22 (24.4)	5 (11.1)	
Pancreatic duct diameter			
Median pancreatic duct diameter (mm)	3.5 (1–15)	4(1–6)	0.89
≤3 mm	32 (35.6)	10 (22.2)	0.12
>3 mm	58 (64.4)	35 (77.8)	
Pancreatic texture			
Firm	61 (67.8)	36 (80)	0.13
Soft	29 (32.2)	9 (20)	
Relation of pancreatic duct to the posterior border			
Median (mm)	5 (1–7)	5 (2–7)	0.25
≤3 mm	32 (35.6)	13 (28.9)	0.51
> mm	58 (64.4)	32 (71.1)	
Method of pancreatic neck division			
Sharp	59 (65.6)	27 (60)	0.31
Diathermy	28 (31.1)	18 (40)	
harmonic	3 (3.3)	0	
Common bile duct diameter (mm)	12 (5–20)	11.5 (7–20)	0.84
Median blood loss (ml)	550 (100–1500)	800 (500–3000)	0.001
Median total operative time (min)	5 (3–7)	5.5 (4–8)	0.004
Type of pancreatic reconstruction			
Duct to mucosa	51 (56.7)	33 (73.3)	0.12
Invagination type	39 (43.3)	12 (26.7)	
Use of internal stent	15 (16.7)	9 (20)	0.67

PD, pancreaticoduodenectomy.

surgery centers, it remains a challenge. POPF remains the most significant and important postoperative complication [1–4].

Many trials have indicated that several variables affect postoperative morbidities after PD, including age, sex, clinical presentation, BMI, liver condition, preoperative biliary drainage, intraoperative blood loss, friability of pancreatic stump, pancreatic duct diammeter, length of the operation, the technique of pancreatic reconstruction, minimally invasive PD, use of postoperative octreotide, and surgeon experience. Pancreatic specialists examine the efficacy of a number of strategies to decrease postoperative morbidities after PD. Such techniques include enhancing surgical performance, pharmacological prophylaxis, and careful selection of patients in certain environmental factors [1–3,11–14].

Only very few studies evaluate the effect of living at high altitudes on the surgical outcomes of major surgeries [10]. This research is intended to determine periampullary tumor surgical outcomes of PD.

DGE is one of the most common problems after PD. Although the ISGPS guidelines are stringent with respect to the description and grading of DGE, the etiology is not discussed [17–21]. Two types of DGE exist: primary type and secondary type DGE. Patients were diagnosed as having primary DGE when there is no clear etiology and no evidence of intraabdominal collections. Patients were diagnosed with obvious etiology as secondary DGE and when connected with any signs of intraabdominal collections. In these cases, several theories were hypothesized in a trial to explain the pathogenesis of primary DGE which includes antroduodenal ischemia, low levels of plasma motilin, peripancreatic inflammation, gastrojejunostomy twist, severe lymphadenectomy, and pancreatic fibrosis [17–21]. In this study, primary DGE was significanty higher in high altitude.

At high altitude, sympathetic dysfunction, hypocarbia, chronic hypoxic pulmonary vasoconstriction, right ventricular hypertrophy, and both systemic and pulmonary hypertension are associated with increased. Some authors hypothesized that high altitudes may be associated with postoperative infectious levels, including surgical site infection, urinary tract infection, and pneumonia, based on the inverse relation between oxygen level and altitude [22,23]. In our study, pulmonary complications were

Table 3 Postoperative data

Variables	PD in normal altitude	PD in high altitude	*P* values
Hospital stay (days)	12 (6–64)	13 (13–55)	0.13
ICU stay (days)	1 (123)	1 (1–25)	0.47
Drain removal (days)	7 (5–50)	7 (6–50)	0.82
Time to resume (days)	6 (4–14)	6 (4–22)	0.06
POD 1 drain amylase	125 (40–4100)	182 (40–6000)	0.39
POD 7 drain amylase	47.5(10–8000)	50 (10–12000)	0.52
POD 1 bilirubin	2 (0.5–30)	2.2 (1–7)	0.2
POD 5 bilirubin	1.3 (0.5–13)	1.4 (0.8–4.5)	0.12
POD 1 albumin	2.7 (2–3.4)	2.8 (1.9–3.5)	0.47
POD 5 albumin	3 (1.8–3.7)	3.1 (1.8–3.9)	0.84
POD 1 WBC	8 (5–20)	8 (5–14)	0.34
POD 5 WBC	7 (5–17)	8 (5–22)	0.71
Total patients with complications	38 (42.2)	25 (55.6)	0.14
Complications grade			
I	21 (23.3)	10 (22.2)	0.3
II	7 (7.8)	4 (8.9)	
III	7 (7.8)	6 (13.3)	
IV, V	3 (3.3)	5 (11.1)	
Postoperative pancreatic leakage POPF	7 (7.8)	4 (8.9)	0.82
Grade B	5	1	0.31
Grade C	2	3	
Pancreatitis	3 (3.3)	3 (6.7)	0.38
Biliary leakage	9 (10)	3 (6.7)	0.52
Delayed gastric emptying	10 (11.1)	12 (26.7)	0.02
Primary	0	6	0.002
Secondary	10	6	
GJ leakage	3 (3.3)	2 (4.4)	0.75
Obstructed GJ	1 (1.1)	0	0.48
Internal hemorrhage	1 (1.1)	0	0.48
Wound infection	5 (5.6)	6 (13.3)	0.12
Burst abdomen	2 (2.2)	1 (2.2)	1
Pulmonary complications	7 (7.8)	9 (20)	0.04
Bleeding GJ	2 (4.4)	0	0.04
DVT	3 (3.3)	6 (13.3)	0.03
Pulmonary embolism	1 (1.1)	5 (11.1)	0.008
Re-exploration	4 (4.4)	2 (4.4)	1
Hospital mortality	3 (3.3)	5 (11.1)	0.07
pulmonary embolism	0	4	0.03
SIRS due to POPF	3	1	
Median survival (months)	20	19	0.39
1 year	87	78	
2 year	67	64	

DVT, deep venous thrombosis; GJ, gastrojejunostomy; PD, pancreaticoduodenectomy; WBC, white blood cells.

significantly higher in high altitude. Wound infection is higher in high altitude but not reaching the significant value.

Much evidence has shown an increase in features leading to a high-altitude triad of Virchow (hypercoagulability, venous stasis, and injury of vessels wall) [24,25]. Some evidence has proposed that alterations in the high-altitude coagulation profile can lead to the start of the cascade of coagulation and cause DVT. Recent findings in high-altitude patients, including elevated red blood cells, thrombocytosis, elevated platelet activation, and elevated plasma fibrinogen coupled with hypoxia and dehydration, result in a thrombotic condition predisposing patients to increased venous thromboembolism [24–27]. In this study, DVT and PE were significantly higher in high altitudes. Numerous research studies showed that extended therapy with low-molecular-weight heparin (LMWH) or nonfraction heparin with pneumatic compression decreases the occurrence of VTE in patients undergoing orthopedic surgery, but its effectiveness or usefulness in abdominal surgery is

Table 4 Postoperative pathology

Variables	PD in normal altitude	PD in high altitude	*P* values
Site of the tumor			
Ampullary	54 (60)	23 (51.1)	0.23
Pancreatic head mass	10 (11.1)	11 (24.4)	
Lower CBD	12 (13.3)	9 (20)	
Duodenal	9 (10)	0	
Pancreatic head mass with uncinate process	5 (5.6)	2 (4.4)	
Type of pathology			
Adenocarcinoma	77 (85.6)	32 (71.1)	0.11
Neuroendocrinal tumor	0	2 (4.4)	
Cholangiocarcinoma	12 (13.3)	9 (20)	
Intraductal papillary mucinous neoplasm (IPMN)	0	2 (4.4)	
Solid pseudopapillary tumor (SPT)	1 (1.1)	0	
No. of dissected LN	12 (5–23)	12 (3–23)	0.75
No. of LN infiltrated	2 (0–4)	1 (0–4)	0.37
Pancreatic safety margin			
R0	86 (95.6)	41 (91.1)	0.59
R1	4 (4.4)	4 (8.9)	
R2	0	0	
Perivascular infiltration	50 (55.6)	26 (57.8)	0.88
Perineural infiltration	47 (52.2)	24 (53.3)	0.76

CBD, common bile duct; LN, lymph node; PD, pancreaticoduodenectomy.

less well anchored. The recommendations of the National Health and Medical Research Council suggest extending LMWH prophylaxis for up to 28 days in high-risk patients who undergo abdominal or pelvic cancer surgery [28,29].

In this study, hospital mortality was higher in high altitude. The main cause was PE in high-altitude region. Over time, the reduction in hospital mortality after PD is the most influential achievement of PD. It is less than 3–5% in specialized high-volume centers. The most common causes of hospital mortality included sepsis secondary to POPF, cardiac causes, PE, severe respiratory dysfunction, uncontrolled bleeding, liver cell failure, and failure to rescue [1,17,28–33]. Silber *et al.* [29] first identified failure to rescue, as a patient's death due to a major postoperative complication. It was proven that fatal complications occur more frequently in low-volume centers than in high-volume centers (29–33). El Amrani *et al.* [32] concluded that in addition to the higher occurrence of septic and thromboembolic morbidities if such morbidities arise, more patients would die in low-volume centers than in high-volume centers. FTR is high after pancreatectomy and is positively linked to hospital volume, illustrating variability in the postoperative management of complications. FTR-rate calculation should become a requirement for performance management services. Male sex, old age, large BMI, ECOG score Over 1, an annual hospital volume of less than 30 PD, and a diagnosis of periampullary cancer were significantly linked with increased FTR ratio [30,31].One inspiring finding of this analysis is that there was no substantial difference between the two groups regarding tumor biology and pathological characteristics.

Our analysis has some limitations due to the retrospective nature of data collection, but since 2000 patients' data were reported in a prospectively controlled database and a propensity score study was well matched. Second, the operations were performed by many surgeons and different centers, which could have been a source of bias. However, overcoming this is aided by the fact that these surgeons and centers had nearly equal levels of trial experience. Third, the sample size is small because the sample of high-altitude patients has been small for the past 3 years. More studies with a larger sample size are therefore required to confirm the effect of high altitudes on PD surgical outcomes.

Conclusion

There is no significant difference regarding POPF frequency and grade between high altitude and normal-altitude regions. Primary DGE is a significant high-altitude complication after PD. High altitude was related to a high incidence of venous thromboembolism, DVT, and PE after PD. Hospital mortality at high altitude was higher, and PE was the principal cause. For patients with PD at high altitudes, prolonged postoperative therapy with

LMWH is recommended for 28 days to decrease the occurrence of postoperative PE and mortality.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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