Austin Journal of Surgery

Open Access

Austin Publishing Group

Research Article

Preoperative and Postoperative Risk Factors of Pancreatic Fistula after Pancreatoduodenectomy-A Retrospective Analysis

Yunkun Cao[1], Guangbing Li[1], Yantian Xu[1], Jianping Wang[1], Xihan Liu[2] and Jun Liu[1]*

[1]Department of Liver Transplantation and Hepatobiliary Surgery, Shandong Provincial Hospital Affiliated to Shandong University, China

[2]Department of Medicine, Shandong University, China

***Corresponding author:** Jun Liu, Department of Liver Transplantation and Hepatobiliary Surgery, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, Shandong, China

Received: March 01, 2019; **Accepted:** March 20, 2019; **Published:** March 27, 2019

Abstract

Background: To investigate the risk factors of Pancreatic Fistula (PF) after Pancreatoduodenectomy (PD) and to summarize the strategies for early diagnosis, prevention, and treatment.

Methods: Retrospective analysis was performed for clinical data of the 203 patients who underwent PD between October 2009 and October 2015. Clinical, surgical, and pathological characteristics were collected. The patients were divided into the PF group and the control group. Analyses were performed to identify the risk factors for PF after PD.

Results: The overall complication incidence was 27.6% (56/203) and the incidence of pancreatic fistula was 9.9% (20/203). The patients with PF showed a higher frequency of preoperative serum bilirubin ≥171 μmol/L, preoperative serum albumin <35 g/L, postoperative serum albumin <35 g/L, soft texture of the pancreas, and diameter of the pancreatic duct <3 mm, as well as higher BMI. There were no differences in gender, age, history of diabetes, operation time, blood loss, and blood transfusion between the two groups.

Conclusion: Patients with PF after PD showed a higher frequency of preoperative serum bilirubin ≥171 μmol/L, preoperative serum albumin <35 g/L, postoperative serum albumin <35 g/L, soft texture of the pancreas, and diameter of the pancreatic duct <3 mm, as well as higher BMI.

Keywords: Pancreatoduodenectomy; Pancreatic fistula; Postoperative complications; Factor analysis

Introduction

Pancreatoduodenectomy (PD) is a major and complex abdominal surgery. During PD, a part of the pancreas, the lower end of the nearby common bile duct, a part of the stomach, and the upper ends of the duodenum and jejunum are resected; in addition, the common bile duct, pancreatic duct, stomach, and jejunum are anastomosed [1,2]. In 1909, Kaush performed the first case of PD in Germany. Since the late 20th century, PD has been extensively developed, and it has become the preferred surgery for lower end of the common bile duct tumors, pancreas head tumors, and duodenal periampullary tumors [3].

Though the incidence of surgical complications has significantly reduced as well [3-5], the incidence of postoperative complications is still as high as 20-70% [6-8]. Because these procedure often performed on people suffering from malnutrition, impaired liver function, and poor general condition, [9] Post pancreaticoduodenectomy complications include Pancreatic Fistula (PF), biliary fistula, abdominal bleeding, and abdominal infection. Among these complications, PF is the most common and fatal complication. There are two main manifestations of PF: 1) pancreatic anastomotic leakage, which refers to trypsin activated by intestinal juice in the intestinal cavity entering into the abdominal cavity from the weakness of the stoma or from incompletely sealed anastomosis; 2) pure leakage of pancreatic juice [10]. According to ISGPF grades, post Pancreaticoduodenectomy Pancreatic Fistula (POPF) were graded as Grade A, B and C. Grade B and C POPF can lead to fatal complications, such as abdominal infection and bleeding, while the Grade A can heal by itself [10]. Early-stage symptoms of PF may include abdominal distension, abdominal pain, fever, and increased abdominal drainage fluid and amylase levels in the drainage fluid were three times of the Upper Limit of Normal (ULN) three days after surgery and the daily amount of fluid is >50 ml [11-15].

Documents showed that POPF is 5-25% and the mortality is 20-40% [16-18]. The causes of POPF are complex. Risk factors include gender, age, history of diabetes, operation time, amount of intraoperative bleeding, amount of intraoperative transfusion, pathological diagnosis, preoperative serum bilirubin levels, preoperative serum albumin levels, postoperative serum albumin levels, texture of the pancreas, and diameter of the pancreatic duct [11-14].

Early diagnosis of PF after PD is important, but in clinical practice, the prevention of postoperative pancreatic fistula is more important, and could effectively improve the survival of the patients and their postoperative quality of life [10]. Therefore, the present study aimed to investigate the risk factors of PF after PD and to summarize the strategies for early diagnosis, prevention, and treatment.

Liu et al. © All rights are reserved

Citation: Cao Y, Li G, Xu Y, Wang J, Liu X and Liu J. Preoperative and Postoperative Risk Factors of Pancreatic Fistula after Pancreatoduodenectomy-A Retrospective Analysis. Austin J Surg. 2019; 6(6): 1174.

Table 1: Complications after PD.

Type of complications	N*
Systemic complications	
Respiratory failure	3(3)
Septic shock	3(3)
Local complications	
Pancreatic fistula	20
Biliary fistula	7
Intra-abdominal infection	25
Abdominal hemorrhage	6(2)
Gastrointestinal hemorrhage	5(1)
Intrahoracic infection	25
Stress ulcer	4
Delayed gastric emptying	3
Other minor complications	9

*The numbers inside the brackets are the number of deaths.

Materials and Methods

Ethic statement

The study protocol was approved by the ethics committee of the Shandong Provincial Hospital Affiliated to Shandong University. All participants or relatives provided a written informed consent for their inclusion in the data analysis.

Study design and patients

This was a retrospective analysis of 203 patients who underwent PD in the hepatobiliary Department and Organ Transplantation Center of Shandong Provincial Hospital between October 2009 and October 2015. The inclusion criteria were: 1) pathological diagnosis of periampullary carcinoma; and 2) underwent PD. The exclusion criteria were: 1) incomplete medical chart.

Data collection

Based on the literature about PF after PD and clinical practices of our center, the following variables were selected to perform statistical analysis [11-14]: patient characteristics (gender, age, history of diabetes, preoperative serum bilirubin levels, and preoperative serum albumin levels), operative data (operation time, amount of intraoperative blood loss, amount of intraoperative transfusion, texture of the pancreas, and diameter of pancreatic duct), and postoperative data (serum albumin levels and pathological diagnosis). The texture of pancreatic were assessed using methods as described [19].

Clinical staging for the patients with malignant tumors was based on the sixth edition of the TNM staging [20]. The diagnostic criteria for PF after PD were: 1) meeting the diagnostic criteria by the International Study Group on Pancreatic Fistula (ISGPF) [21]; 2) amylase levels in the drainage fluid that are still >3 times the Upper Limit of Normal (ULN) three days after surgery and if the daily amount of fluid is >50 ml; or 3) leakage of pancreatic juice by imaging examination.

Preoperative preparation

Preoperative relevant auxiliary examinations were performed. Liver and kidney function and blood coagulation were examined. Active treatment was performed for patients combined with other disease, and related departments were asked to assist the treatment. Functions of major organs were examined and evaluated. Chest X-ray examination was performed and patients with metastatic lesions were excluded. The nutritional status of the patients was improved, and electrolyte imbalance was corrected. Hepatoprotective treatment was performed for patients with obstructive jaundice. Injection of vitamin K or plasma transfusion was performed to improve the coagulation function. Prophylactic use of antibiotics was performed before the operation. All patients with jaundice did not receive Percutaneous Transhepatic Cholangial Drainage (PTCD) or Endoscopic Nasal Biliary Drainage (ENBD). For patients with chronic diseases (such as diabetes and hypertension), blood glucose and blood pressure were controlled before the operation.

Pancreaticoduodenectomy

PD was performed as previously described [9,11,22-25].

Postoperative management

Routine treatments included liver protection, anti-inflammation, acid suppression, fluid replacement therapy, and maintenance of the water-electrolyte and acid-base balances. After the operation, enteral nutrition was supplemented as early as possible. Somatostatin was routinely administered. Serum albumin (10-30 g) was administrated for patients with low serum albumin levels before the operation and the patients with low serum albumin levels after the operation. The drainage tube was removed for patients without PF and biliary fistula after no liquid outflew from the abdominal drainage tube. For patients with obstructed drainage of PF and biliary fistula, percutaneous peritoneal drainage was performed.

Statistical analysis

All patients were divided into the PF group and the control group based on whether they met criteria for postoperative PF. For continuous data meeting the normal distribution (according to the Kolmogorov-Smirnov test), Analysis of Variance (ANOVA) was used to compare the groups. If the data did not meet the normal distribution, the Wilcoxon rank sum test was used. Categorical data were analyzed using the Fisher exact test. SPSS 19.0 (IBM, Armonk, NY, USA) was used for statistical analysis. Two-sided P-values <0.05 were considered to be statistically significant.

Results

Characteristics of the patients

There were 126 males and 77 females, for a male-to-female ratio of 1.64:1. The patients were 37-84 (mean, 62.9) years of age. There were 71 (71/203, 34.9%) patients with distal bile duct cancer, 60 (60/203, 29.6%) with pancreatic head carcinoma, 39 (39/203, 19.2%) with periampullary cancer, 30 (30/203, 14.8%) with malignant tumor of the duodenum, and 3 (3/203, 1.5%) of benign pancreatic head tumor. There were 100 patients whose serum albumin levels were low (<35 g/L) and 113 whose Total Bilirubin Levels (TBIL) were high (≥171 μmol/L). There were 130 patients whose carbohydrate antigen 19-9 levels (CA19-9) were high (>40 U/ml) and 195 whose Carcinoembryonic Antigen Levels (CEA) were high (>5 μg/L).

Table 2: Factors associated with PF.

Factors	PF n=20	P
Gender		0.14
Male	11 (55.0%)	
Female	9 (45.0%)	
Age(years)	61	0.25
History of diabetes		0.18
Yes	11 (55.0%)	
No	9 (45.0%)	
Preoperative serum bilirubin levels		0.01
<171μmol/L	2 (10.0%)	
≥171μmol/L	18 (90.0%)	
Preoperative serum albumin levels		0.03
≥35g/L	5 (25.0%)	
<35g/L	15 (75.0%)	
Postoperative serum albumin levels		0.01
≥35g/L	5 (25.0%)	
<35g/L	15 (75.0%)	
Operation time		0.35
≥6h	13 (65.0%)	
<6h	7 (35.0%)	
Amount of intraoperative blood loss (ml)	400.5±100.0	0.25
Amount of intraoperative transfusion (ml)	500.6±120.3	0.15
Texture of the pancreas		0.02
Hard	3 (15.0%)	
Soft	17 (85.0%)	
Diameter of the pancreatic duct		0.03
≥3mm	6 (30.0%)	
<3mm	14 (70.0%)	
Body mass index (kg/m^2)	23.8±3.6	0.008

Postoperative PF and other complications

Table 1 showed the complications after PD. There were 20 patients (9.9%) suffered POPF. Nine patients died post PD. The causes of death were as follow: respiratory failure (n=3), septic shock (n=3), abdominal hemorrhage (n=2), and gastrointestinal hemorrhage (n=1).

Associations between clinical factors and postoperative PF

Table 2 presents the analyses of the factors associated with PF. The patients with PF showed a higher frequency of preoperative serum bilirubin ≥171 μmol/L (90.0% *vs.* 51.9%, P=0.01), preoperative serum albumin <35 g/L (75.0% *vs.* 46.4%, P=0.03), postoperative serum albumin <35 g/L (75.0% *vs.* 48.1%, P=0.01), soft texture of the pancreas (85.0% *vs.* 37.2%, P=0.02), and diameter of the pancreatic duct <3 mm (70.0% *vs.* 41.0%, P=0.03), as well as higher BMI (23.8±3.6 *vs.* 22.4±3.5 kg/m^2, P=0.008). There were no differences in gender, age, history of diabetes, operation time, blood loss, and blood transfusion between the two groups.

Table 3: Pathological characteristics of malignant tumors with PF.

Factors	Controls n=181	P
Depth of tumor invasion		0.1
Limited to the base layer	49 (27.1%)	
Full-thickness	92 (67.4%)	
Full-thickness and surrounding organ	10(5.5%)	
Tumor size		0.99
≥3cm	73(40.3%)	
<3cm	104(59.7%)	

Associations between pathological factors and postoperative PF

In the present series, there were 200 cases with malignant tumors. There were no differences in depth of tumor invasion and tumor size between the two groups (Table 3).

Discussion

The causes of PF after PD are complex, and PF may lead to other complications. In addition, risk factors vary among available studies [13,14,18,24,26]. Therefore, this study aimed to investigate the risk factors of PF after PD and to summarize the strategies for early diagnosis, prevention, and treatment. The results showed that the patients with PF showed a higher frequency of preoperative serum bilirubin ≥171 μmol/L, preoperative serum albumin <35 g/L, postoperative serum albumin <35 g/L, soft texture of the pancreas, and diameter of the pancreatic duct <3 mm, as well as higher BMI.

Previous studies have shown that relevant factors related to the incidence of PF after PD include gender, age, history of diabetes, operation time, amount of intraoperative bleeding, amount of blood transfusion, pathological diagnosis, preoperative serum bilirubin levels, preoperative serum albumin levels, postoperative serum albumin levels, texture of the pancreas, and diameter of the pancreatic duct [11-14]. However, these risk factors vary among studies and countries. Hu et al. [14] showed that male gender, high BMI, anastomosis type, small pancreatic duct diameter, and soft pancreas were risk factors for PF after PD. Lerut et al. [27] showed that emergency of the procedure, age, serum bilirubin, quality of the pancreatic tissue, and renal insufficiency were associated with PF. Liu et al. [13] showed that small pancreatic duct diameter was a risk factor for PF. On the other hand, Matsusue et al. [17] showed that no factor apart age was associated with PF after PD. Van Bergen Henegouwen et al. [23] showed that only small pancreatic duct size and ampullary carcinoma diagnosis were associated with PF after PD. Finally, Yang et al. [24] showed that only the pancreatic duct size and pancreatic tissue texture affected the incidence of PF. In the present study, duodenal tumors, diameter of the pancreatic duct <3 mm, internal pancreatic drainage, external pancreatic drainage, soft texture of the pancreas, and BMI were associated with the incidence of PF after PD. Discrepancies among studies may be due to a number of factors, including ethnicity, surgical experience, and economic status, among others.

Matsusue et al. [17] has found that patient age >70 years old is a risk factor for pancreatic fistula, [17] supported by Lerut et al. [27] Older age can be associated with a number of factors leading to poor

surgical outcomes (all types together) such as malnutrition, impaired liver function, and poor general condition [6-8]. In the present study, age was not associated with the incidence of PF after PD.

Lerut et al. [27] showed that the incidence of PF after PD was increased in patients with preoperative total bilirubin levels >102.6 μmol/L. Therefore, it has been suggested that jaundice should first be controlled before PD can be performed. On the other hand, Pisters et al. [28] reported 300 cases of PD, and the results suggest that except an increase of wound infection, the incidence of other complications (including PF) in the jaundice-reducing group was not different from that of the non-jaundice-reducing group [28]. In the present series, no jaundice-reducing treatments were given before PD. In the PF group, there were [18] (90.0%) patients with high preoperative total bilirubin levels (≥171 μmol/L), while 51.9% of the controls had elevated total bilirubin. Nevertheless, the discrepancy among studies could be used to the methods of measuring total bilirubin, as well as to the cut-off levels used.

Low preoperative serum albumin levels reflect the degree of liver damage [29]. Hypoproteinemia can affect anastomotic healing [30] because of reduced tissue regeneration and repair. In the present study, 75% of the patients with PF had low albumin levels before surgery compared to 46.4% in controls.

Many studies have reported that the texture of pancreas is an important factor affecting the occurrence of PF after PD [10,14,17,18,24]. It may be because that a soft pancreas will increase of difficulty of anastomosis and increased space between threads of suture is likely to cause leakage of pancreatic juice, thereby resulting in PF. This kind of pancreas is easy to be lacerated when performing PD. Yeo et al. [15] reported that the incidence of PF of patients with hard pancreas was lower than for the patients with soft pancreatic parenchyma. In the present study, there were three patients with hard texture of pancreas and PF, accounting for 15.0% of the patients with PF, compared to 62.8% in the control group.

Many studies showed that a high risk factor for PF is a pancreatic duct with a diameter <3 mm, [13,14,23,24] leading to difficult suture and the end-to-side anastomosis with the jejunal mucosa cannot be directly performed. Moreover, due to the secretion of pancreatic juice, it is difficult to heal if the anastomosis is lost. Pancreatic juice secreted by the pancreas contains a large amount of proteolytic enzymes, and the tissue around the anastomosis can be digested. In this study, there were 114 patients with pancreatic duct diameter >3 mm, and there were six patients (5.3%) with PF, compared to 15.7% among the patients with a pancreatic duct diameter <3 mm.

In the present study, both internal and external drainage were associated with PF after PD, but external drainage was associated with a higher risk of PF. Meng et al. [31] showed that external drainage was associated with a lower likelihood of PF after PD. This discrepancy could be due to a number of factors, including the characteristics of the patients and diseases, and the surgical experience, among others.

The present study has some limitations. The sample size was small and from a single center. In addition, the retrospective nature of the study limited the variables that could be evaluated. Additional studies are necessary to adequately determine the risk factors for PF after PD.

Conclusion

In conclusion, patients with PF showed a higher frequency of preoperative serum bilirubin >171 μmol/L, preoperative serum albumin <35 g/L, postoperative serum albumin <35 g/L, soft texture of the pancreas, and diameter of the pancreatic duct <3 mm, as well as higher BMI.

Acknowledgment

This study was supported by the Mechanisms of wip1/NF-kB on prevention SFSS after living donor liver transplantation (NSFC 81373172).

References

1. Fingerhut A, Vassiliu P, Dervenis C, Alexakis N, Leandros E. What is in a word: Pancreatoduodenectomy or pancreaticoduodenectomy? Surgery. 2007; 142: 428-429.
2. Michalski CW, Weitz J, Buchler MW. Surgery insight: surgical management of pancreatic cancer. Nat Clin Pract Oncol. 2007; 4: 526-535.
3. Are C, Dhir M, Ravipati L. History of pancreaticoduodenectomy: early misconceptions, initial milestones and the pioneers. HPB (Oxford). 2011; 13: 377-384.
4. de Wilde RF, Besselink MG, van der Tweel I, de Hingh IH, van Eijck CH, Dejong CH, et al. Impact of nationwide centralization of pancreaticoduodenectomy on hospital mortality. Br J Surg. 2012; 99: 404-410.
5. Iqbal N, Lovegrove RE, Tilney HS, Abraham AT, Bhattacharya S, Tekkis PP, et al. A comparison of pancreaticoduodenectomy with pylorus preserving pancreaticoduodenectomy: a meta-analysis of 2822 patients. Eur J Surg Oncol. 2008; 34: 1237-1245.
6. Razumilava N, Gores GJ. Cholangiocarcinoma. Lancet. 2014; 383: 2168-2179.
7. Hidalgo M. Pancreatic cancer. N Engl J Med. 2010; 362: 1605-1617.
8. Lieberman DA. Clinical practice. Screening for colorectal cancer. N Engl J Med. 2009; 361: 1179-1187.
9. Riediger H, Makowiec F, Fischer E, Adam U, Hopt UT. Postoperative morbidity and long-term survival after pancreaticoduodenectomy with superior mesenterico-portal vein resection. J Gastrointest Surg. 2006; 10: 1106-1115.
10. Suzuki Y, Fujino Y, Tanioka Y, Hiraoka K, Takada M, Ajiki T, et al. Selection of pancreaticojejunostomy techniques according to pancreatic texture and duct size. Arch Surg. 2002; 137: 1044-1047.
11. Shrikhande SV, Qureshi SS, Rajneesh N, Shukla PJ. Pancreatic anastomoses after pancreaticoduodenectomy: do we need further studies? World J Surg. 2005; 29: 1642-1649.
12. Haddad LB, Scatton O, Randone B, Andraus W, Massault PP, Dousset B, et al. Pancreatic fistula after pancreaticoduodenectomy: the conservative treatment of choice. HPB (Oxford). 2009; 11: 203-209.
13. Liu QY, Zhang WZ, Xia HT, Leng JJ, Wan T, Liang B, et al. Analysis of risk factors for postoperative pancreatic fistula following pancreaticoduodenectomy. World J Gastroenterol. 2014; 20: 17491-17497.
14. Hu BY, Wan T, Zhang WZ, Dong JH. Risk factors for postoperative pancreatic fistula: Analysis of 539 successive cases of pancreaticoduodenectomy. World J Gastroenterol. 2016; 22: 7797-7805.
15. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg. 1997; 226: 248-257.
16. Gouillat C, Chipponi J, Baulieux J, Partensky C, Saric J, Gayet B. Randomized controlled multicentre trial of somatostatin infusion after pancreaticoduodenectomy. Br J Surg. 2001; 88: 1456-1462.
17. Matsusue S, Takeda H, Nakamura Y, Nishimura S, Koizumi S. A prospective

analysis of the factors influencing pancreaticojejunostomy performed using a single method, in 100 consecutive pancreaticoduodenectomies. Surg Today. 1998; 28: 719-726.

18. Sato N, Yamaguchi K, Chijiiwa K, Tanaka M. Risk analysis of pancreatic fistula after pancreatic head resection. Arch Surg. 1998; 133: 1094-1098.

19. Marchegiani G, Ballarin R, Malleo G, Andrianello S, Allegrini V, Pulvirenti A, et al. Quantitative Assessment of Pancreatic Texture Using a Durometer: A New Tool to Predict the Risk of Developing a Postoperative Fistula. World J Surg. 2017; 41: 2876-2883.

20. AJCC. Cancer Staging Manual, 6th edition. Chicago: American Joint Committee on Cancer. 2002.

21. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an International Study Group (ISGPF) definition. Surgery. 2005; 138: 8-13.

22. de Castro SM, Busch OR, van Gulik TM, Obertop H, Gouma DJ. Incidence and management of pancreatic leakage after pancreatoduodenectomy. Br J Surg. 2005; 92: 1117-1123.

23. van Berge Henegouwen MI, De Wit LT, Van Gulik TM, Obertop H, Gouma DJ. Incidence, risk factors, and treatment of pancreatic leakage after pancreaticoduodenectomy: drainage *versus* resection of the pancreatic remnant. J Am Coll Surg. 1997; 185: 18-24.

24. Yang YM, Tian XD, Zhuang Y, Wang WM, Wan YL, Huang YT. Risk factors of pancreatic leakage after pancreaticoduodenectomy. World J Gastroenterol. 2005; 11: 2456-2461.

25. Warshaw AL, Thayer SP. Pancreaticoduodenectomy. J Gastrointest Surg. 2004; 8: 733-741.

26. Marcus SG, Cohen H. Ranson JH. Optimal management of the pancreatic remnant after pancreaticoduodenectomy. Ann Surg. 1995; 221: 635-645.

27. Lerut JP, Gianello PR, Otte JB, Kestens PJ. Pancreaticoduodenal resection. Surgical experience and evaluation of risk factors in 103 patients. Ann Surg. 1984; 199: 432-437.

28. Pisters PW, Hudec WA, Hess KR, Lee JE, Vauthey JN, Lahoti S, et al. Effect of preoperative biliary decompression on pancreaticoduodenectomy-associated morbidity in 300 consecutive patients. Ann Surg. 2001; 234: 47-55.

29. Vincent JL. Relevance of albumin in modern critical care medicine. Best Pract Res Clin Anaesthesiol. 2009; 23: 183-191.

30. Iancu C, Mocan LC, Todea-Iancu D, Mocan T, Acalovschi I, Ionescu D, et al. Host-related predictive factors for anastomotic leakage following large bowel resections for colorectal cancer. J Gastrointestin Liver Dis. 2008; 17: 299-303.

31. Meng G, Xing Q, Yuan Q, Du Z, Wang Y, Meng h. Internal compared with external drainage of pancreatic duct during pancreaticoduodenectomy: a retrospective study. Chin J Cancer Res. 2014; 26: 277-284.

Austin J Surg - Volume 6 Issue 6 - 2019
ISSN : 2381-9030 | www.austinpublishinggroup.com
Liu et al. © All rights are reserved

Citation: Cao Y, Li G, Xu Y, Wang J, Liu X and Liu J. Preoperative and Postoperative Risk Factors of Pancreatic Fistula after Pancreatoduodenectomy-A Retrospective Analysis. Austin J Surg. 2019; 6(6): 1174.