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Research Progress on Common Complications after Pancreaticoduodenectomy

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Abstract: ***Pancreaticoduodenectomy (PD), also known as pancreaticoduodenectomy, is a major surgical treatment for some severe hepatobiliary diseases. During the operation, not only is it necessary to explore the abdominal cavity for the patient, but also to help the patient with the resection of the duodenum and the reconstruction of the digestive tract. Each step is particularly important [1]. This surgery requires the resection of multiple organs and the completion of complex digestive tract reconstruction, with high operational difficulty and a high rate of postoperative complications. It is one of the most challenging surgeries in the field of abdominal surgery. Laparoscopic pancreaticoduodenectomy (LPD) was first reported by Gagner and Pomp in 1994. In the early stage, it was limited due to high postoperative complication and mortality rates, as well as no advantages in terms of hospital stay and cost [2]. LPD is one of the most complex laparoscopic surgeries, involving the resection of multiple organs, large surgical trauma, and complex digestive tract reconstruction steps, with a high incidence of postoperative complications. Therefore, in the early stage of LPD, its safety and effectiveness were widely questioned due to high postoperative mortality and severe complications. In recent years, with the improvement of laparoscopic techniques and the continuous update of surgical instruments, LPD has developed rapidly and has become a routine surgical method in some large pancreatic surgery centers in China [3]. Recent retrospective clinical studies have shown that LPD has the advantages of less bleeding and faster postoperative recovery, and its postoperative complication rate, mortality rate, and oncological treatment effect are similar to or even better than those of traditional open surgery [4-8]. Postoperative complications are very likely to occur in patients, and clinical studies suggest that this situation usually occurs within one week after surgery. Patients may experience significant abdominal distension, abdominal tenderness, and even a certain degree of high fever. An increase in the volume of abdominal drainage fluid can be found when performing abdominal drainage for the patient. If the amylase level in the patient's abdominal drainage fluid increases, it can be confirmed that the patient has developed a pancreatic fistula. Generally, non-surgical methods are chosen for treatment. Different methods of digestive tract reconstruction also have their own value in preventing the occurrence of pancreatic fistula [9]. PD is a surgical operation with high technical difficulty, complex operation, and a high rate of postoperative complications. The classic Whipple procedure and various modified procedures have become safe and effective treatment methods. However, the high perioperative mortality rate has long hindered the promotion of this surgery [10]. With the improvement of surgical techniques, standardized perioperative care and complication management, the postoperative mortality rate of PD has dropped to less than 5% [11]. This has expanded its indications from pancreatic cancer to cystic tumors, neuroendocrine tumors, and other uncommon tumors. However, the overall perioperative complication rate of PD still ranges from 30% to 60%, which seriously affects the quality of life of patients and increases medical costs [12]. Accurate preoperative assessment and standardized surgical procedures can effectively reduce the incidence of postoperative complications [13]. Active, reasonable, and effective management of postoperative complications is crucial for improving the short-term prognosis of patients. This article systematically introduces common postoperative complications of PD based on domestic and foreign literature and the clinical experience of our center.***

Keywords: Pancreaticoduodenectomy, Complications, Pancreatic fistula, Bleeding, Delayed gastric emptying, Postoperative bile leakage.

1. Postoperative Pancreatic Fistula (PF)

Pancreatic fistula (PF) is the most common complication leading to death after PD. Uncontrolled pancreatic fistula caused by failure of pancreaticojejunostomy can be catastrophic, resulting in delayed gastric emptying, abdominal abscess formation, or massive bleeding due to vascular erosion, and has been reported to increase hospital mortality by 3 times [14]. According to the ISGPS definition, this complication can be divided into two main categories: biochemical leakage, which does not require clinical management, and postoperative pancreatic fistula, which requires clinical management (i.e., grades B and C). Various approaches have been tried to reduce the risk of PF and reduce damage. Early treatment was through direct re-laparotomy, irrigation and drainage, and when necessary, total resection of the pancreas to completely remove the source of sepsis. However, this treatment modality has a high mortality rate [15,16]. Among many methods, the most controversial is how to choose the placement of abdominal drainage tube. Although many studies have shown that routine placement of abdominal drainage does not reduce complication rates and may even lead to increased complications. A generally accepted theory is that the drainage tube as an entry point can lead to an increased risk of postoperative infection because the drainage tube itself can act as a foreign body to cause an inflammatory response that affects wound healing. However, at present, the routine placement of abdominal drainage tube after PD in most centers in the world is still the routine practice, which is considered to be the key to control the external drainage of pancreatic fistula and monitor the formation of pancreatic fistula [17]. Once pancreatic fistula occurs, it may lead to secondary abdominal infection and bleeding. If it is not treated in time, it will lead to serious systemic complications and even life risk. Many factors can affect the occurrence of pancreatic fistula after PD, including patient's own factors (age, jaundice and nutritional status), disease-related factors (lesion location, pancreatic texture, main pancreatic duct diameter), and surgery-related factors (pancreatic stump treatment, digestive tract reconstruction method and operator experience, etc.) [18]. Zhang Bo et al. [19]. The study showed that pancreatic duct diameter was an independent risk factor for postoperative pancreatic fistula. The incidence of pancreatic fistula in patients with pancreatic

duct <3 mm was 38.46%, while the incidence of pancreatic fistula in patients with pancreatic duct ≥3 mm was only 11.0%. Moreover, it has been shown that pancreatic duct <3 mm is an independent risk factor not only for postoperative pancreatic fistula, but also for grade B and C pancreatic fistula [20]. It has been reported in domestic literature that advanced age (age >65 years) is an independent risk factor for pancreatic fistula after PD [21]. However, it has also been shown that age does not affect the occurrence of postoperative pancreatic fistula [22]. Whether pancreatic texture, anastomosis method and preoperative total bilirubin level are risk factors for postoperative pancreatic fistula is also inconsistent in the literature, which needs to be determined by multi-center and prospective studies.

2. Postpancreatectomy Haemorrhage (PPH)

PPH is the most critical complication after PD. Although its diagnosis is relatively clear and the overall incidence is not high, the mortality related to PPH can be as high as 38% [23], which seriously threatens the life safety of patients. The International Study Group on Pancreatic Surgery (ISGPS) defines PPH based on three key parameters: time of onset, site of bleeding, and clinical severity. According to the time of onset, bleeding was defined as “early” PPH if it occurred within 24 hours after surgery. PPH was defined as “late” if it occurred after 24 hours after surgery. In terms of severity grading, ISGPS classifies PPH into grades A, B and C based on factors such as the decrease of hemoglobin, the need for blood transfusion, and the manifestation of bleeding in the cavity (such as in the digestive tract) or outside the cavity (such as in the abdominal cavity), among which grade C is the most serious and often requires intervention or surgical intervention [24]. Postoperative bleeding is another serious complication after PD. Although with the continuous progress of surgical techniques and perioperative management, the overall incidence has shown a downward trend, however, the bleeding-related mortality and the risk of postoperative rebleeding are still high [25]. Therefore, the clinical should still be on high alert for bleeding after PD and should not be ignored. From the analysis of the relationship between bleeding mechanism and time, early bleeding is directly related to surgical procedures, and the common causes are gastrointestinal anastomotic bleeding or pancreaticoenteric anastomotic bleeding, mainly caused by insufficient intraoperative hemostasis. Late hemorrhage is more often associated with postoperative complications, especially postoperative pancreatic fistula and intra-abdominal infection, which can corrode peripheral blood vessels (such as the stump of gastroduodenal artery) and cause life-threatening bleeding. In terms of preoperative clinical risk factors, it has been suggested that preoperative liver function status is closely related to the risk of postoperative bleeding. For example, there is evidence that abnormal elevation of preoperative transaminase level (≥172 U/L) and significant elevation of total bilirubin level (≥159 μmol/L) are important risk factors for postoperative bleeding [26], and some studies have shown that preoperative total bilirubin level is also an independent risk factor after PD. Most patients undergoing PD are accompanied by obstructive jaundice, which further affects coagulation function and leads to postoperative bleeding. However, whether preoperative drainage of jaundice is necessary to reduce the incidence of postoperative bleeding and other complications is still inconclusive, and further research is needed. In addition, other preoperative factors were explored. Studies have pointed out that male gender and smaller pancreatic duct diameter are independent risk factors for late postoperative hemorrhage after PD in patients with demographic and anatomical characteristics [27]. In addition to the above preoperative factors, complications in the course of postoperative period are the key contributing factors for hemorrhage. A large number of studies have confirmed that postoperative pancreatic fistula (POPF) and intra-abdominal infection are clear risk factors leading to postoperative bleeding, especially delayed and dangerous bleeding [28]. Once pancreatic fistula or severe intra-abdominal infection occurs, the corrosive effect of digestive fluid or infection on surrounding blood vessels may lead to rupture of vascular stump, causing sudden and massive intra-abdominal or gastrointestinal bleeding. This kind of condition is often dangerous, and it is necessary to stop bleeding by means of vascular interventional embolization or reoperation in time, otherwise it will directly endanger the patient’s life. In conclusion, postoperative hemorrhage after PD is a multifactorial and dynamically developing serious complication. Its prevention and management should run through the whole perioperative period, including careful evaluation and optimization of coagulation function and biliary status before operation, accurate and thorough hemostasis during operation, and active prevention and treatment of complications such as pancreatic fistula and infection after operation. Further studies are needed to more accurately identify high-risk patients, optimize preoperative preparation strategies, and establish a standardized hierarchical management process to ultimately reduce the incidence of this complication and its related mortality.

3. Delayed gastric Emptying (DGE)

DGE is common after PD, which is more common in pylorus-preserving pancreaticoduodenectomy (PPPD). Dge usually occurs within 1 to 2 weeks after PD. Although DGE is not urgent in most cases, it can increase patient discomfort, prolong hospital stay, and increase hospitalization costs [29]. The pathogenesis of DEG is still a medical problem. Duodenectomy and right gastric artery ligation lead to pyloric spasm and reduce plasma motilin levels, which is considered to be the most likely cause of DEG after PD [30]. Some studies have found that intra-abdominal infection is an independent risk factor for delayed gastric emptying through multivariate analysis, which may be due to the reduced function of gastric wall and celiac nerve plexus in patients with intra-abdominal infection, inhibiting gastrointestinal peristaltic waves [31], and then causing paralytic ileus and delayed gastric emptying, increasing the risk of delayed gastric emptying. Some studies also showed that the implementation of PTCD (percutaneous bile duct puncture) significantly increased the risk of delayed gastric emptying after surgery, which may be due to abdominal adhesion and inflammation caused by PTCD puncture [32]. Intraoperative factors may be the main factors for delayed gastric emptying. Such as improper alignment of digestive tract reconstruction, poor healing, anastomotic torsion, angulation, etc. The current surgical methods mainly include classic Whipple surgery, laparoscopic surgery, robotic surgery, pylorus-preserving pancreaticoduodenectomy, and different gastrointestinal

anastomosis. Compared with open pancreaticoduodenectomy, laparoscopic pancreaticoduodenectomy has the advantages of smaller incision, less intraoperative blood loss and faster recovery. It is generally believed that laparoscopic approach is safe and feasible under the premise of rich clinical experience of doctors [33]. Postoperative abdominal complications are considered to be one of the important factors of DGE, and their mechanisms may include gastrointestinal ischemia and external blood stimulation caused by abdominal bleeding, gastrointestinal dysfunction caused by inflammatory factors or toxins caused by abdominal infection or abscess, and DGE induced by inflammation or infection caused by pancreatic fistula and biliary fistula [34]. Walsh et al. [35] showed that postoperative hypoproteinemia may lead to delayed gastric emptying, which may be due to postoperative malnutrition and hypoproteinemia, which may cause tissue edema around the anastomosis, and poor healing may cause weak gastric motility and lead to DGE. Therefore, albumin and red blood cell transfusion should be considered for patients with poor nutritional status to correct hypoproteinemia and anemia, so as to reduce tissue edema and DGE incidence. In addition, early feeding before fasting time may aggravate the burden of gastrointestinal function, and postoperative drug use and postoperative stress may also affect the recovery of gastric peristalsis. At present, there is no specific treatment for delayed gastric emptying, so it is particularly important to prevent delayed gastric emptying after surgery. The identification of risk factors and early treatment may be the key to reduce the occurrence of delayed gastric emptying. Careful preoperative evaluation is an important measure to reduce the incidence of DGE and ensure perioperative safety. It is necessary to carefully ask the patient's medical history and physical condition, assess the risk of postoperative DGE, and control preoperative blood pressure, blood glucose and creatinine within a safe range to ensure the safety of surgery and reduce the incidence of postoperative complications.

4. 4. Postoperative biliary fistula

Biliary fistula is A relatively rare complication after PD. The overall incidence of biliary fistula is about 1.3% in the clinical data of our center, and all of them were grade A biliary fistula with mild clinical impact, and they were successfully cured after conservative treatment such as maintaining patency of drainage. Its mechanism is closely related to the anatomical conditions of the patient's own bile duct (such as the small diameter and weak wall of the bile duct) and the technical accuracy of bilioenteric anastomosis during the operation, among which bilioenteric anastomotic leakage is the most common. The clinical manifestations and severity of biliary fistula mainly depend on the duration of biliary fistula, daily fistula volume, whether it is complicated with bacterial infection, and the location and patency of abdominal drainage tube. If the amount of fistula is small and the drainage is sufficient, the patient usually has no obvious clinical symptoms. On the contrary, if the amount of fistula is large and the drainage is not adequate, the accumulation of bile in the abdominal cavity can lead to localized or diffuse peritonitis, which is manifested as peritoneal irritation signs such as fever, abdominal pain, abdominal distension, abdominal tenderness, and rebound pain. In severe cases, it can even cause septic shock, which is life-threatening. At present, there are relatively limited reports in the literature on biliary fistula after PD. The study of Duconseil et al. [36] pointed out that biliary fistula with a daily drainage volume of less than 100 mL can usually be self-healed by maintaining unobstructed drainage without special intervention. However, if the patient has signs of infection such as peritonitis, sepsis, or the daily drainage volume exceeds 1000 mL, it may suggest that there may be a large biliary tract injury or drainage obstruction, and timely intervention by means of endoscopy, intervention or reoperation is needed. Other literature has shown that preoperative or intraoperative biliary decompression measures may help to reduce the incidence of overall postoperative complications, pancreatic fistula and abdominal infection [37]. In addition, the causes of postoperative pancreatic fistula mainly included the following technical factors: (1) the suture was not tight enough during pancreaticojejunostomy, or the suture cut the pancreatic tissue resulting in local tear; (2) The length of the pancreatic stump into the jejunum is insufficient, if it is less than 3 cm, it is easy to leak due to incomplete wrapping; (3) Poor blood supply of the jejunal stump used for anastomosis, or excessive tension at the anastomosis, leading to local ischemia, necrosis and even anastomotic dehiscence; (4) Improper management of the pancreatic duct, such as failure to clearly identify the broken end of the pancreatic duct and perform appropriate mucomucosal anastomosis or stent placement before pancreaticojejunostomy, is one of the key links to prevent pancreatic leakage [38]. Therefore, careful operation during operation, ensuring blood supply and tension free state of anastomosis, and correct treatment of pancreatic duct are important technical guarantees to reduce the incidence of pancreatic leakage.

5. 5. Abdominal infection

Studies [39-41] have shown that the occurrence of intra-abdominal infection after PD is affected by a variety of preoperative, intraoperative and postoperative factors. Preoperative risk factors mainly included whether to undergo biliary drainage, diabetes, hypoproteinemia and other basic diseases. Intraoperative factors such as blood transfusion volume, operation time and operation precision are also related to the risk of infection. Postoperative complications, especially pancreatic fistula, are considered to be one of the key links leading to intra-abdominal infection. Once abdominal infection occurs after PD, it can not only induce or aggravate other complications such as pancreatic fistula and biliary fistula, but also significantly prolong the length of hospital stay, increase medical costs, and even lead to multiple organ failure and eventually lead to death [42,43]. In a retrospective analysis of 408 PD patients, Sugiura et al. [44] found that pancreatic fistula was the strongest independent risk factor for postoperative intra-abdominal infection. Data from this study showed that the incidence of postoperative intra-abdominal infection was as high as 76% in patients with pancreatic fistula, compared with 26% in patients without pancreatic fistula. The results of our study were consistent with the above conclusions: the incidence of intra-abdominal infection in patients with pancreatic fistula was 59.2%, which was much higher than that in patients without pancreatic fistula (11.3%). Multivariate analysis confirmed that clinically significant pancreatic fistula (clinically relevant pancreatic fistula) was one of the independent risk factors for

intra-abdominal infection after PD. There is a pathological relationship between pancreatic fistula and intra-abdominal infection, which promotes and causes each other. On the one hand, when pancreatic fistula occurs after PD, pancreatic juice rich in digestive enzymes accumulates in the abdominal cavity, which can erode surrounding tissues, damage blood vessels and anastomotic stoma, and cause local inflammation and barrier destruction. At the same time, surgical trauma, immunosuppression, and increased risk of intestinal flora translocation can promote the occurrence of intra-abdominal infection. On the other hand, in the state of intra-abdominal infection, inflammatory mediators such as phospholipase and lipopolysaccharide produced by bacteria can activate trypsinogen in pancreatic juice, further aggravating the self-digestion effect of pancreatic enzymes on surrounding tissues, forming a vicious circle of local tissue necrosis and infection spread [44-46]. Therefore, pancreatic fistula and intra-abdominal infection are intertwined and aggravated in the pathological process, which significantly increases the complexity of clinical treatment and the risk of poor prognosis.

6. Summary and Outlook

Pancreaticoduodenectomy (PD) is the core surgical procedure for the treatment of periampullary and pancreatic head diseases, and its technical complexity and perioperative management are among the highest in abdominal surgery. Despite advances in surgical techniques, equipment and perioperative management strategies, the indications for PD have been broadened and perioperative mortality has decreased significantly. However, the incidence of postoperative complications (such as pancreatic fistula, bleeding, delayed gastric emptying, bile leakage and intra-abdominal infection) remains high, which seriously restricts the short-term rehabilitation and long-term prognosis of patients. Various complications are often interrelated and causal with each other, forming complex clinical syndromes, increasing the difficulty of diagnosis and treatment. Therefore, a systematic understanding of the mechanism, risk factors, and prevention and treatment strategies of complications is essential for improving the outcome of PD patients. In the future, the research and practice in this field should be further promoted in the following directions: (1) Precise risk assessment and individualized intervention: using multi-omics data, imaging features and clinical indicators to construct a more accurate preoperative prediction model, identify high-risk patients, and realize early warning and individualized preventive intervention of complication risk. (2) Standardization and optimization of surgical techniques: Continue to explore and standardize the key technical aspects of minimally invasive procedures such as laparoscopy and robotics, especially the optimization and innovation of digestive tract reconstruction methods (such as pancreaticojejunostomy and bilioenteric anastomosis), so as to reduce the risk of pancreatic fistula, bile leakage and other complications from the source. (3) Multidisciplinary collaboration and process of complication management: establish and promote a standardized complication management pathway with pancreatic surgery as the center, covering multidisciplinary teams such as critical care medicine, interventional radiology, clinical nutrition, and infection control. For critical complications such as bleeding and severe infection, a standard of rapid response and hierarchical diagnosis and treatment should be established. (4) Transformation and application of new diagnosis and treatment technologies: to explore the application value of new drainage materials, local hemostatic materials and biological glue in the prevention and treatment of complications, and to study the best intervention time and plan of minimally invasive techniques such as endoscopy and intervention in the treatment of complications. (5) Focus on patient-reported outcomes and long-term quality of life: in research and clinical practice, we should not only pay attention to the incidence of complications and short-term mortality, but also pay attention to the long-term impact of complications on patients' nutritional status, physiological function and mental health, and optimize the whole-process management strategy based on this. Through the deepening of basic research, the improvement of clinical technology and the integration of management mode, it is expected to further reduce the incidence and severity of postoperative complications of PD, and finally achieve the synchronous improvement of patients' survival time and quality of life.

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