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**FIELD OF VISION**

- 1546** SARS-COV-2 infection (coronavirus disease 2019) for the gastrointestinal consultant
Hajifathalian K, Mahadev S, Schwartz RE, Shah S, Sampath K, Schnoll-Sussman F, Brown Jr RS, Carr-Locke D, Cohen DE, Sharaiha RZ

OPINION REVIEW

- 1554** Optimized timing of using infliximab in perianal fistulizing Crohn's disease
Sun XL, Chen SY, Tao SS, Qiao LC, Chen HJ, Yang BL

REVIEW

- 1564** Intestinal epithelial barrier and neuromuscular compartment in health and disease
D'Antongiovanni V, Pellegrini C, Fornai M, Colucci R, Blandizzi C, Antonioli L, Bernardini N
- 1580** Gastrointestinal cancer stem cells as targets for innovative immunotherapy
Chivu-Economescu M, Necula LG, Matei L, Dragu DL, Neagu AI, Alexiu I, Bleotu C, Diaconu CC

MINIREVIEWS

- 1594** Is the measurement of drain amylase content useful for predicting pancreas-related complications after gastrectomy with systematic lymphadenectomy?
Nakanishi K, Kanda M, Sakamoto J, Kadera Y

ORIGINAL ARTICLE**Basic Study**

- 1601** Silymarin, boswellic acid and curcumin enriched dietetic formulation reduces the growth of inherited intestinal polyps in an animal model
Girardi B, Pricci M, Giorgio F, Piazzolla M, Iannone A, Losurdo G, Principi M, Barone M, Ierardi E, Di Leo A

Retrospective Cohort Study

- 1613** Lifestyle factors and long-term survival of gastric cancer patients: A large bidirectional cohort study from China
Zhao LL, Huang H, Wang Y, Wang TB, Zhou H, Ma FH, Ren H, Niu PH, Zhao DB, Chen YT

Retrospective Study

- 1628** Optimal treatment strategies for hepatic portal venous gas: A retrospective assessment
Gonda M, Osuga T, Ikura Y, Hasegawa K, Kawasaki K, Nakashima T
- 1638** Clinical and microbiological characteristics of patients with biliary disease
Gu XX, Zhang MP, Zhao YF, Huang GM

- 1647** Development and validation of a prediction model for microvascular invasion in hepatocellular carcinoma
Wang L, Jin YXZ, Ji YZ, Mu Y, Zhang SC, Pan SY

Prospective Study

- 1660** Macrophage inhibitory cytokine-1/growth differentiation factor-15 in premalignant and neoplastic tumours in a high-risk pancreatic cancer cohort
O'Neill RS, Emmanuel S, Williams D, Stoita A

CASE REPORT

- 1674** Small bowel racemose hemangioma complicated with obstruction and chronic anemia: A case report and review of literature
Fu JX, Zou YN, Han ZH, Yu H, Wang XJ

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Is the measurement of drain amylase content useful for predicting pancreas-related complications after gastrectomy with systematic lymphadenectomy?

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Abstract

Many studies investigating postoperative pancreatic fistula (POPF) after gastrectomy, including studies measuring drain amylase content (D-AMY) as a predictive factor have been reported. This article reviews previous studies and looks to the future of measuring D-AMY in patients after gastrectomy. The causes of pancreatic fluid leakage are; the parenchymal and/or thermal injury to the pancreas, and blunt injury to the pancreas by compression and retraction. Measurement of D-AMY to predict POPF has become common in clinical practice after pancreatic surgery and was later extended to the gastric surgery. Several studies have reported associations between D-AMY and POPF after gastrectomy, and the high value of D-AMY on postoperative day (POD) 1 was an independent risk factor. To improve both sensitivity and specificity, attempts have been made to enhance the predictive accuracy of factors on POD 1 as well as on POD 3 as combined markers. Although several studies have shown a high predictive ability of POPF, it has not necessarily been exploited in clinical practice. Many problems remain unresolved; ideal timing for measurement, optimal cut-off value, and means of intervention after prediction. Prospective clinical trial could be imperative in order to develop D-AMY measurement in common clinical practice for gastric surgery.

Key words: Gastric cancer; Drain amylase; Postoperative pancreatic fistula; Pancreas-related complications; Gastrectomy; Early prediction

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Core tip: Many studies investigating postoperative pancreatic fistula after gastrectomy, including measurement of drain amylase content (D-AMY) as a predictive factor. This article reviews previous studies and looks to the future of measuring D-AMY in patients

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after gastrectomy. Several studies have reported that the high D-AMY on postoperative day 1 or day 3 was an independent risk factor for postoperative pancreatic fistula. However, issues for clinical use remain unresolved, including the ideal timing of measurement, optimal cut-off value and intervention after prediction. Prospective clinical trials might be indispensable for D-AMY to become a common marker in clinical practice.

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INTRODUCTION

Gastrectomy with radical lymph node dissection, especially peri-pancreatic lymph node dissection, is the mainstay for resectable gastric cancers. Pancreas-related complications, especially postoperative pancreatic fistula (POPF), is one of the most common postoperative complications, and can sometimes lead to serious results, including intra-abdominal abscess, subsequent sepsis, and intraperitoneal bleeding, which usually require prolongation of hospitalization^[1,2].

Many studies predicting POPF after gastrectomy have been investigated and age, operation time, body mass index, total gastrectomy, splenectomy, anatomical position of the pancreas, and high value of drain amylase content (D-AMY) have been reported as substantial predictive factors^[2-13]. Among those, D-AMY, which is the measurement of the amylase content in drained abdominal fluids taken through an indwelling intra-abdominal drain, is promising because it can be measured objectively regardless of the patient's preoperative condition, type of surgical procedure, and surgeon's skill^[14]. However, several problems remain unsolved precluding the implication in common clinical practice.

This article reviews previous reports and looks to the future of measuring D-AMY to predict POPF in gastric cancer surgery.

MECHANISM OF PANCREATIC FLUID LEAKAGE IN GASTRIC CANCER SURGERY

In gastric cancer surgery, the pancreatic duct is not usually transected, and the mechanism of pancreatic fluid leakage after surgery is different from that of pancreatectomy. Mainly, three mechanisms of pancreatic fluid leakage in gastric cancer surgery are reported, presumably caused by the operator and assistant surgeons. The operator can injure the surface of the pancreas by parenchymal and/or thermal injury during the dissection of the suprapancreatic lymph nodes^[15]. Second, the assistant could compress and retract the pancreas to achieve a good view of the suprapancreatic area during suprapancreatic lymph node dissection, so called "blunt injury"^[16]. Ida *et al*^[16] conducted animal experiments using pigs and reported that blunt injury causes pancreatic necrosis and inflammatory cell infiltration, and the value of amylase content around the pancreas increases 2-4 h after the procedure.

Another mechanism is that pancreatic tail mobilization during combined splenectomy or splenectomy with distal pancreatectomy can damage the pancreatic parenchyma, resulting in pancreatic fluid leakage^[3]. However, indications for such extended lymphadenectomy for gastric cancer has recently become limited^[17].

In this regard, pancreatic fluid leakage involving gastric cancer surgery could mostly be minor leakage, that tends to be subsided spontaneously without clinically relevant pancreas-related postoperative complications.

THE BEGINNING OF STUDIES PREDICTING POPF USING DRAIN AMYLASE CONTENT IN PANCREATIC SURGERY

In pancreatic surgery, the measurement of D-AMY is also used in the diagnostic criteria of POPF^[18]. In general, pancreatectomy is recognized as a highly invasive surgery and is associated with a mortality of approximately 5% and a morbidity of 30%-60%^[19]. Approximately 16% of patients develop POPF, making it one of the common complications of pancreatectomy^[20]. The clinical stratification of POPFs was established by the International Study Group on Pancreatic Fistula (ISGPF) definition in 2005^[18]. The presence of POPFs can be determined on postoperative day (POD) 3 by the amylase content in the drained fluid; therefore, the measurement of D-AMY has become common in clinical practice in the field of pancreatic surgery. After pancreatectomy, pancreatic fluid leakage is caused by a disruption of the main pancreatic duct, and D-AMY directly reflects pancreatic fluid leakage^[21,22]; therefore, the measurement of D-AMY is a reasonable prediction tool for pancreas-related complications. This concept was later extended to gastric cancer surgery; however, the mechanisms responsible for pancreatic fluid leakage are supposed to differ between pancreatectomy in which the main pancreatic duct is transected, and gastrectomy, which causes some problems. The source of pancreatic fluid leakage after gastrectomy is the seepage of pancreatic juice from the parenchymal damage of the pancreas and blunt damage by compression or retraction^[15,16]. Even if the value of D-AMY is high on POD 3, this minor pancreatic leakage seems to subside spontaneously without proceeding to clinical fistula formation^[3]. Thus, the establishment of a gastric cancer surgery-specific definition and prediction tool for POPF is desirable.

DEFINITION OF POPF IN GASTRIC CANCER SURGERY

Despite clinical importance, POPF had not been uniformly defined until 2005 when the ISGPF established the definition based on the clinical impact of POPF-related complications^[18], and it has been well accepted in the pancreatic surgery community. The stratifications are as follows: Grade A, pancreatic fistulas with no clinical impact, although D-AMY on or after POD 3 is three times more than the upper normal serum amylase level; grade B requires a change in management or adjustment in the clinical pathway; and grade C requires a major change in clinical management and aggressive clinical intervention. This ISGPF classification is sometimes applied in the gastric cancer surgery community. However, validation of applying this definition to POPF following gastrectomy still remains unclear. As described in the previous section, the mechanisms of pancreatic fluid leakage in gastric cancer surgery are different from those in pancreatic surgery, and are shown in [Figure 1](#); POPF of ISGPF grade A is not necessarily clinically significant; in other words, POPF with no clinical impact need not be defined in gastric cancer surgery. In addition, almost all POPFs in gastric cancer surgery are classified as ISGPF grade B, and ISGPF grade C is very rare.

As another definition of POPF, the Clavien-Dindo classification has been adopted, which is a comprehensive evaluation of postoperative complications and has gained widespread acceptance^[23,24]. This classification system regards grade II or higher as clinically relevant and grade III or higher as severe complications. However, this definition is sometimes inconsistent with clinical severity, although objective and simple. For example, replacement of drainage tubes under fluoroscopy is classified as Clavien-Dindo grade IIIa, despite minor changes in clinical management and regarded severe complications.

An establishment of a new grading system of POPF after gastrectomy may be necessary. However, it is less frequently used and may not be familiar because the prevalence of POPF after gastrectomy is not as high compared with that after pancreatectomy; it occurs in approximately 1.6% of patients who underwent distal gastrectomy^[25] and in 2.6% of patients who underwent total gastrectomy^[26]. At present, the ISGPF and Clavien-Dindo classification systems have each of their advantages and disadvantages, and it is desirable to use both appropriately.

LITERATURE SEARCH OF STUDIES REPORTING PREDICTIVE VALUE FOR POPF USING DRAIN AMYLASE CONTENT IN GASTRIC CANCER SURGERY

Several studies have reported associations between D-AMY and POPF after gastrectomy, and [Table 1](#) shows these studies in the gastric cancer surgical field. In

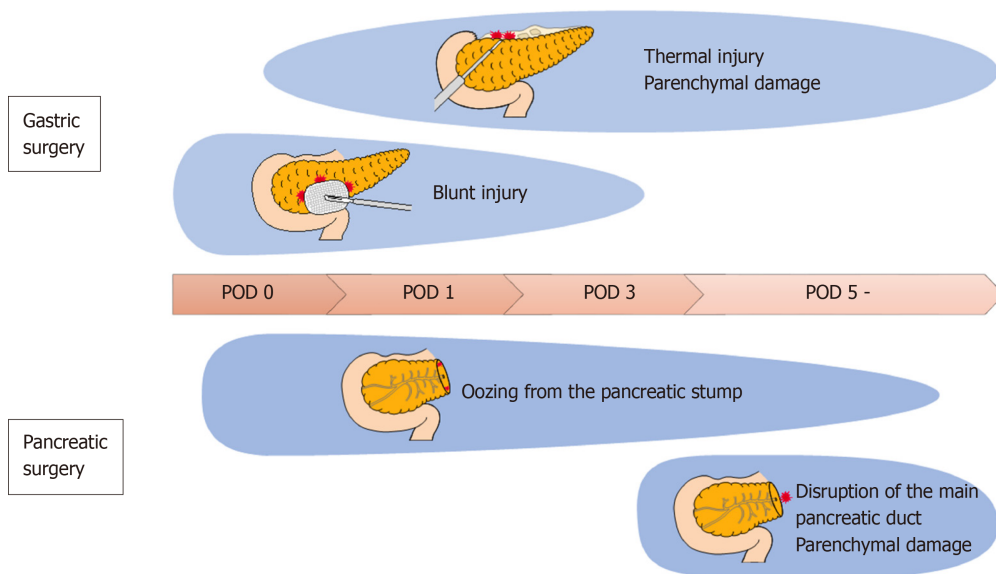


Figure 1 Mechanisms and timings of pancreatic fluid leakage in gastric and pancreatic surgery. POD: Postoperative day.

1997, Sano *et al*^[3] reported for the first time that the measurement of D-AMY was useful for POPF after gastrectomy. However, a definition of POPF had not been established at that time, and their study defined it as a condition in which the D-AMY level was more than three times the upper normal serum amylase level for more than 7 d after operation. In their study, the prevalence of POPF in patients with D-AMY ≥ 4000 IU/L on POD 1 was significantly higher compared with that in patients with D-AMY < 4000 IU/L on POD 1, indicating the high level of D-AMY on POD 1 was retained to POD 7, regardless of clinically relevant complications.

The ISGPF established the definition of POPF in 2005, and Iwata *et al*^[2] adapted this definition and reported associations between D-AMY and POPF after gastrectomy in 2010. They reported that the prevalence of ISGPF grade A or higher was 16.3% and that D-AMY ≥ 1000 U/L on POD 1 along with body mass index were independent risk factors for POPF. However, the study suffered from the inclusion of a broad spectrum of surgical procedures ranging from the laparoscopic approach for early-stage cancer to extended lymphadenectomy accompanied by splenectomy for advanced cancer. In 2011, there were two studies that defined ISGPF grades B or C as POPF. Miki *et al*^[6] reported that the prevalence of POPF after total gastrectomy with D2 lymphadenectomy was 22.1% and that D-AMY ≥ 3398 IU/L on POD 1 was an independent predictor of POPF. Tomimaru *et al*^[4] reported that the prevalence of POPF after total gastrectomy with D1 plus or D2 lymphadenectomy was 9.2% and that D-AMY ≥ 5000 IU/L on POD 1 was a predictor of POPF. The above three studies were validated by applying the ISGPF classification and the predictive ability of D-AMY on POD 1, but the surgical procedures were different among studies, which caused the prevalence of POPF and the cut-off values to be inconsistent. In 2012, Kobayashi *et al*^[7] adapted the Clavien-Dindo classification and reported that D-AMY ≥ 2000 IU/L on POD 1 and C-reactive protein ≥ 20 mg/dL on POD 3 were predictive of Clavien-Dindo classification grade III or higher POPF. The Clavien-Dindo classification grade III or higher POPF is the same as the ISGPF grade B or higher (grade C) excluding antibiotic treatment. So far, we summarized the studies to evaluate the predictive value of D-AMY on POD 1.

Two time point measurements of D-AMY have been developed to enhance the predictive value of POPF. In 2016, Kanda *et al*^[8] reported that D-AMY on POD 1 served as a predictive factor for POPF. In addition, patients whose D-AMY level on POD 3 was retained at $\geq 31.2\%$ of that on POD 1 were more likely to develop POPF after laparoscopic distal gastrectomy^[8]. After that, two studies reported that the combined use of D-AMY on POD 1 and POD 3 had a higher predictive performance for POPF compared with each alone^[9,10]. The combined use had high sensitivity; however, it did not serve as an early prediction.

A few studies have considered drainage volume^[5,27] and concluded that drainage volume was not significant in gastric cancer surgery.

Table 1 Studies measuring drain amylase content for predicting postoperative pancreatic fistula after gastrectomy in patients with gastric cancer

Ref.	Sample size	Surgical procedure	POD 1		POD 3		Definition of POPF
			Data available	Cut-off	Data available	Cut-off	
Sano <i>et al</i> ^[3] , 1997	102	OTG, D1 - \geq D2	Yes	4000 IU/L	No	NG	D-AMY > 3 times more than S-AMY for \geq 7 days
Iwata <i>et al</i> ^[2] , 2010	372	Gastrectomy, D1 - \geq D2	Yes	1000 IU/L	No	NG	ISGPF definition (grade A/B/C)
Tomimaru <i>et al</i> ^[4] , 2011	172	TG, D1 plus - D2	Yes	5000 IU/L	No	NG	ISGPF definition (grade B/C)
Miki <i>et al</i> ^[6] , 2011	104	TG, D2	Yes	3398 IU/L	No	NG	ISGPF definition (grade B/C)
Kobayashi <i>et al</i> ^[7] , 2015	448	Gastrectomy, D1 - \geq D2	Yes	1949 IU/L	No	NG	C-D classification (grade III or higher)
De Sol <i>et al</i> ^[5] , 2015	53	Gastrectomy, D2	No	NG	Yes	D-AMY > 3 times more than S-AMY	ISGPF definition (grade B/C)
Kanda <i>et al</i> ^[8] , 2016	265	LDG, D1 plus - D2	Yes	904 IU/L	Yes	Retained at \geq 31.2% of D-AMY on POD 1	C-D classification (grade II or higher)
Taniguchi <i>et al</i> ^[9] , 2017	591	Gastrectomy D1- \geq D2	Yes	2900 IU/L	Yes	2100 IU/L	ISGPF definition (grade B/C)
Kamiya <i>et al</i> ^[10] , 2018	801	Gastrectomy D1 plus - \geq D2	Yes	2218 IU/L	Yes	555 IU/L	C-D classification (grade III or higher)
Wakahara <i>et al</i> ^[12] , 2019	327	Gastrectomy D0- D2	No	NG	Yes	761 IU/L	C-D classification (grade II or higher)

POPF: Postoperative pancreatic fistula; POD: Postoperative day; OTG: Open total gastrectomy; D-AMY: Amylase content of drainage tube; S-AMY: Serum amylase content; ISGPF: International Study Group on Pancreatic Fistula; NG: Not given or reported in the study; TG: Total gastrectomy; C-D classification: Clavien-Dindo classification; LDG: Laparoscopic distal gastrectomy.

REMAINING PROBLEMS FOR FUTURE STUDIES

As described in the previous section, the definition of POPF has not been established; in addition, several problems have remained for clinical use, such as timing of measuring D-AMY, optimal cut-off value, and means of intervention after early prediction.

The timing of measuring D-AMY has not been determined. There is a dilemma between early prediction and diagnostic accuracy. With a single predictive marker, there is a limitation to increasing both sensitivity and specificity, and attempts have been made to enhance the predictive accuracy of factors on POD 1 as well as on POD 3 as combined markers^[8-10]. However, it has limited clinical use for early prediction and early intervention. In other words, the timing of measurement that has both high diagnostic accuracy and early detection has not been determined.

Second, the cut-off values were different among studies. Differences in the definition of POPF, differences in the surgical procedure, and small-scale retrospective studies prevent the establishment of the optimal cut-off value. From the viewpoint of the mechanism of POPF, the differences in surgical procedures do not affect fistula formation. A large-scale prospective trial is warranted to establish an optimal cut-off value that applies to any surgical procedure.

Third, it is unclear whether early intervention will improve outcomes even if early prediction is successful. Prophylactic antibiotics in gastric cancer surgery are usually administered until the next morning after surgery. Additional prophylactic antibiotic administration may be beneficial for preventing deterioration in particular POPF high-risk patients who underwent pancreaticoduodenectomy^[28]; although so far, the benefit is unclear in gastric cancer surgery^[29]. Currently, a prospective exploratory randomized trial to evaluate prolonged prophylactic antibacterial drug treatment for patients with high levels of D-AMY on POD 1 after gastrectomy is in progress (UMIN000012152). In addition, the benefit of the measurement of D-AMY content as an indicator of early drainage tube removal is unknown. The prophylactic drain is helpful for the detection of not only POPF but also other serious complications,

including anastomotic leakage, intraoperative bleeding, and injury of the intestine. It is possible that the drainage of intra-abdominal fluids, including pancreatic juice, may prevent subsequent POPF^[2]. From the viewpoint of the enhanced recovery after surgery program, the drainage tube should be removed as soon as it is deemed unnecessary in order to reduce drain-related complications and shorten the hospital stay after gastrectomy^[30-32]. Additionally, unnecessary drain placement is harmful in terms of intra-abdominal fluid loss. At present, the measurement of D-AMY is not used as an indicator of early drainage tube removal, but if the level of D-AMY is low, the drainage tube can be removed with little concern for later pancreas-related complications.

CONCLUSION

The measurement of D-AMY is promising because of its high predictive ability of POPF, even in the gastric cancer surgical field. However, many problems remain unresolved, *i.e.*, definition of POPF, ideal timing for measurement, optimal cut-off value, and means of intervention after prediction. Prospective clinical trial could be imperative in order to develop D-AMY measurement in common clinical practice for gastric surgery.

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