

## ARTÍCULO ORIGINAL

# Ascitic fluid amylase-to-serum amylase ratio to predict pancreatic duct leaks causing ascites

## Relación amilasa líquido ascítico versus sérica para predecir ascitis secundaria a daño del ducto pancreático

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### Author contribution

RW: conception and design, writing. AAQ: statistical analysis and interpretation of data. PD: critical revision of the article for important intellectual content. KM: editing, critical revision of the article for important intellectual content. PY: critical revision of the article for important intellectual content. ViK: critical revision of the article for important intellectual content. VaK: conception and design reviewing, editing.

### Conflict of interest

The authors deny any conflict of interest. The authors have nothing to declare.

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### ABSTRACT

**Objectives:** Pancreatic duct leaks can cause ascites, and fluid amylase can be used as a marker to suggest pancreatic duct leak; however, there is no reference parameter or cutoff value for diagnosis. We assessed whether a novel ratio of ascitic fluid to serum amylase can reliably predict pancreatic leaks and need for endoscopic retrograde cholangiopancreatography (ERCP). **Materials and methods:** Patients who had fluid amylase from ascitic fluid and serum amylase within one week of confirmed pancreatic leaks via ERCP were included along with appropriate medical and surgical controls. **Results:** A total of sixteen patients were included in the study group. The mean ascitic fluid amylase to serum amylase ratio in the study group was 243, and 0.3511, and 0.9406 for medical and surgical controls respectively. The cutoff ratio to predict pancreatic leaks was 6.89 with 100% sensitivity and specificity (p-value 0.0000000000001347). **Conclusions:** Patients with a fluid to serum amylase ratio of at least 6.89 should be considered high risk for pancreatic leak with consideration to proceed directly to ERCP.

**Keywords:** Cholangiopancreatografía, Endoscopia Retrograda; Pancreáticos Ductos; Ascitis (source: MeSH NLM).

### RESUMEN

**Objetivos:** Las fugas del conducto pancreático pueden causar ascitis, y la amilasa en el líquido puede utilizarse como un marcador para sugerir una fuga del conducto pancreático; sin embargo, no hay un parámetro de referencia ni un valor de corte para el diagnóstico. Evaluamos si una nueva relación entre la amilasa en líquido ascítico y la amilasa sérica puede predecir de manera confiable las fugas pancreáticas y la necesidad de colangiopancreatografía retrógrada endoscópica (CPRE). **Materiales y métodos:** Se incluyeron pacientes que tenían amilasa en líquido ascítico y amilasa sérica dentro de una semana tras la confirmación de fugas pancreáticas mediante CPRE, junto con controles médicos y quirúrgicos apropiados. **Resultados:** Un total de dieciséis pacientes fueron incluidos en el grupo de estudio. La media de la relación entre la amilasa en líquido ascítico y la amilasa sérica en el grupo de estudio fue de 243, y de 0,3511 y 0,9406 para los controles médicos y quirúrgicos, respectivamente. El valor de corte para predecir fugas pancreáticas fue de 6,89, con una sensibilidad y especificidad del 100% (valor p=0,0000000000001347). **Conclusiones:** Los pacientes con una relación de amilasa en líquido a amilasa sérica de al menos 6.89 deben ser considerados de alto riesgo para fugas pancreáticas y se debe considerar proceder directamente a CPRE.

**Palabras clave:** Colangiopancreatografía Retrógrada Endoscópica; Conductos Pancreáticos; Ascitis (fuente: DeCS Bireme).

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## INTRODUCTION

Pancreatic duct leaks are consequences of pancreatitis, trauma, tumors, and iatrogenic causes that pose significant morbidity and mortality to patients <sup>(1)</sup>. Pancreatic leaks can present as: fluid collections, pseudocysts, ascites, fistulae, and walled-off-pancreatic necrosis <sup>(2)</sup>. High fluid amylase levels may be seen in these conditions, but there are currently no specific serum laboratory parameters to diagnose ascites caused by a pancreatic leak. Unfortunately, neither laboratory data nor high-quality cross-sectional imaging alone are diagnostic, and high fluid amylase can be seen in malignancy, peritoneal inflammation, and intestinal perforation <sup>(3)</sup>.

Endoscopic retrograde cholangiopancreatography (ERCP) is considered the gold standard for diagnosis and treatment for pancreatic duct leaks resulting in ascites; however, ERCP carries the risk of serious adverse effects such as perforation and post-procedural pancreatitis <sup>(4)</sup>. Our study aims to determine the ratio of ascitic fluid amylase to serum amylase and the best cut-off value for accurate prediction of pancreatic duct leaks resulting in ascites with high sensitivity and specificity.

## MATERIALS AND METHODS

This was a single-center, observational, unblinded, retrospective study that included all patients with confirmed pancreatic leaks via ERCP who had ascitic fluid and serum amylase within one week of the procedure from 2013-2023. This study was approved by the Carilion Clinic Virginia Tech Institutional Review Board for research on 4/4/2023. Exclusion criteria included patients less than 18 years old and those who underwent total pancreatectomy. Although pancreatic fluid collections and pseudocysts are evidence of pancreatic duct leaks, we chose to strictly include patients who had ascites or free fluid in the abdomen collected by either paracentesis or surgical drains for fluid analysis. Medical and surgical control groups were included for comparison of fluid amylase-to-serum amylase ratios and statistical analysis to produce a predictive value. Medical controls included sixteen patients with known decompensated cirrhosis with ascites. The surgical control group consisted of twenty-one patients who underwent surgical procedures without involvement of the pancreaticobiliary system and had ascites or free fluid.

To assess the predictive power of fluid/serum amylase and ratios regarding pancreatic leaks, Mann-Whitney U test, linear regression, and ROC analyses were conducted on data from 16 patients and 37 controls. The Mann-Whitney U test showed a highly significant p-value ( $p=1.032e-08$ ), indicating a significant difference between the two groups. Linear regression did not reveal statistically significant coefficients for the intercept (-121.42) or the predictor (17.64), both with  $p > 0.05$ . Deviance statistics suggest a well-fitting model (Null deviance: 6.4920e+01, Residual deviance: 7.150e-09). A Receiver Operating Characteristic (ROC) curve, based on a logistic regression model, demonstrated an area under

the curve of 100%, signifying perfect discriminatory ability between controls and cases. The analysis was performed using base statistical methods in R version 4.3.1 and the 'pROC' package for ROC analysis.

## Ethical considerations

IRB Approval: This research study was approved by the IRB on 4/4/2023.

This study was presented as a poster presentation at Digestive Disease Week (DDW) 2024.

## RESULTS

### Demographics

A total of 53 patients were included in the study. Sixteen patients were included in the pancreatic duct (PD) leak group with a mean age of 50 with 12.5% females (N=2) (Table 1). Sixteen patients were included in the medical control group with 68.8% females (N=11) and a mean age of 65.4. The surgical control group consisted of 21 patients with 42.9% females (N=9) with a mean age of 59.3 (Table 2).

**Table 1.** Demographics and characteristics of pancreatic leak group.

Demographics	
Number of pancreatic leaks (N)	16
Mean age	50
Sex female (N)	2 (12.5%)
Comorbidities	
Chronic pancreatitis	3 (18.8%)
Chronic liver disease	4 (25%)
Heart disease	2 (12.5%)
Malignancy	2 (12.5%)
No past medical history	5 (31.3%)
Site of pancreatic leak	
Head	2 (12.5%)
Genu	2 (12.5%)
Body	3 (18.8%)
Tail	5 (31.3%)
Another discontinuous/disrupted duct	4 (25%)
Etiology of leak	
Alcoholic pancreatitis	5 (31.3%)
Trauma	9 (56.3%)
Iatrogenic	2 (12.5%)
Size of stent used	
5Fr x 4cm	2 (12.5%)
5Fr x 5cm	1 (6.25%)
5Fr x 7cm	1 (6.25%)
5Fr x 12cm	3 (18.75%)
6Fr x 14cm	1 (6.25%)
7Fr x 3cm	1 (6.25%)
7Fr x 4cm double pigtail	1 (6.25%)
7Fr x 10cm	2 (12.5%)
7Fr x 15cm pancreaticogastrostomy	1 (6.25%)
7Fr x 25cm pancreaticogastrostomy	1 (6.25%)
7Fr x 14cm	1 (6.25%)

**Table 2.** Demographics and characteristics of medical and surgical controls.

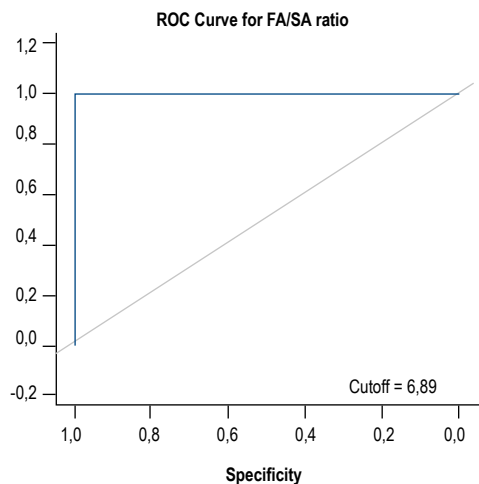
Demographics	Medicine controls	Surgical controls
Number of controls	16	21
Mean Age	65	59
Sex Female (N)	11 (68.8%)	9 (42.9%)
Comorbidities		
Chronic liver disease	16 (100%)	2 (9.5%)
Heart disease	5 (31.3%)	5 (23.8%)
Lung disease	4 (25%)	1 (4.8%)
Malignancy	1 (6.25%)	6 (28.6%)
Metabolic syndrome	3 (18.8%)	4 (19%)
No past medical history	0	4 (19%)

**Characteristics of PD leak group**

Comorbidities and other characteristics of the PD leak group can be seen in Table 1. The most common etiology of PD leak was trauma (N=9). The pancreatic tail was the most common site of PD leak (N=5). Four patients had disconnected/disrupted ducts. Pancreatic sphincterotomy with stent placement was the most common therapeutic management (n=12). Various size stents were used with 5Fr x12cm stent with the highest frequency. Pancreaticogastrostomy was employed for 2 patients. Eleven patients had ascitic fluid collected from surgical drains and five via paracentesis.

**Comparison of fluid and serum amylase**

The mean ascitic fluid amylase (AFA) level was 27,590 U/L in PD leak and 20.7 U/L and 117.7 U/L in medical and surgical controls respectively (Table 3). The mean ascitic fluid amylase to serum amylase ratio (FA/SA) in the PD leak group was 243, and 0.3511, and 0.9406 in the medical and surgical controls respectively. The ratio to predict pancreatic leaks was 6.89 with 100% sensitivity and 100% specificity (p-value 0.0000000000001347) (Figure 1).



**Figure 1.** ROC curve: the ascitic fluid amylase to serum amylase ratio to PD leak is 6.89 with 100% sensitivity and 100% specificity. (p-value 0.0000000000001347) respectively.

**Table 3.** Mean serum amylase, mean ascitic fluid, and mean fluid-to-serum ratio of pancreatic leak, medical, and surgical controls.

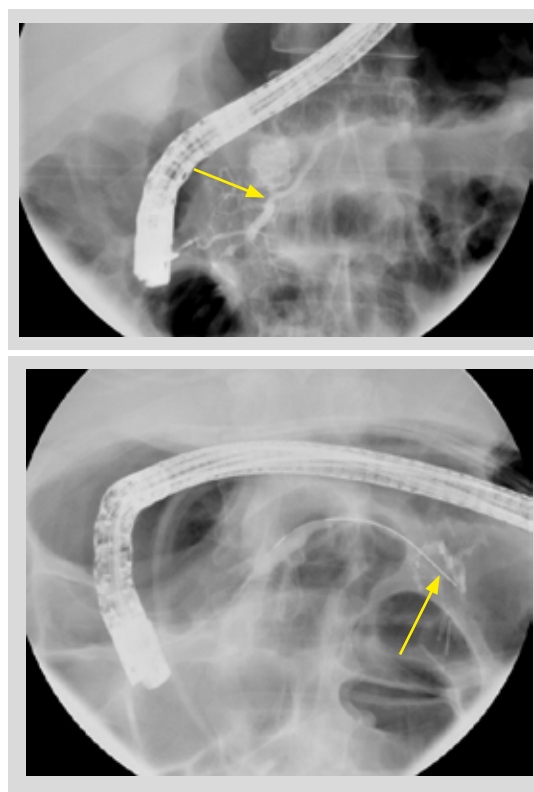
Study group	Pancreatic leak (P)	Medical controls (M)	Surgical controls (S)	p-value
Mean serum amylase (U/L)	183.5	68.4	125.1	0.0731
Mean Ascitic fluid amylase (U/L)	27,590	20.7	117.7	0.0000*
Mean Fluid-to-Serum Amylase Ratio	243	0.351	0.9406	0.0000*

\* For mean fluid amylase, Kruskal-Wallis's (KW) test indicated a difference in the mean (p-value = 9.665e-09)

\* For mean fluid amylase to serum amylase ratio, KW test indicated a difference in the mean (p-value = 9.758e-09)

**DISCUSSION**

Common causes of PD leaks include acute or chronic pancreatitis, trauma, and iatrogenic during surgical procedures (1). PD leaks can be inconspicuous in nature, and can present as fluid collections, pseudocysts or pancreatic ascites. High-quality cross sectional imaging like computed tomography (CT) or magnetic resonance imaging (MRI) are frequently obtained to assist in the diagnosis of PD leaks; however, these imaging modalities are imprecise and cannot confirm diagnosis in all cases such as early pancreatic trauma as well as small duct leaks (5). Additionally, these imaging modalities are not dynamic, unlike ERCP, which can provide live visualization of a PD leak with contrast extravasation during pancreatography (5) (Figure 2).



**Figure 2.** ERCP with pancreatography showing a duct leak in the body (top) and tail (bottom).

Amylase is a pancreatic enzyme that is secreted during digestion, but it is also present in other tissues such as salivary glands and reproductive organs. Elevation of amylase is one of the diagnostic criteria for acute pancreatitis<sup>(2)</sup>. When pancreatic duct trauma occurs, leakage of amylase is expected, and the use of laboratory values to aid in the diagnosis can be helpful, as in the case of diagnosing pancreatic fistulas after pancreatic surgeries<sup>(6)</sup>. Patients who have abdominal surgery may have placement of Jackson-Pratt (JP) drains. Fluid amylase from these drains can be analyzed, and concern for pancreatic duct leak can arise if the amylase is very high; however, a diagnostic cut off value for elevated amylase has not been clearly established. Also, interpretation of elevated amylase can be difficult when there are other confounding factors such as trauma, abdominal surgery, and/or malignancy. Therefore, ERCP becomes a necessary but risky modality to diagnose the PD leak.

While pseudocysts, fluid collections, and abscesses represent evidence of contained PD leaks, needle aspiration is required to obtain a fluid sample. Our study specifically includes patients with pancreatic ascites to analyze fluid samples to predict PD leak and need for ERCP. ERCP is considered the gold standard for diagnosis and treatment of PD leaks; however, it does not come without risks and potential complications such as a risk of post-procedural pancreatitis up to 10%<sup>(4,7)</sup>. When PD leaks require therapeutic management, ERCP has been effective and successful as shown in retrospective studies<sup>(8)</sup>.

Our results demonstrate that using the ascitic fluid amylase to serum amylase ratio can be used as a predictive, noninvasive tool for diagnosing pancreatic duct leaks causing ascites. Average fluid amylase in the PD group was much higher when compared with the medical or surgical controls. The ascitic fluid amylase to serum amylase ratio when compared among the medical and surgical control group was 6.89, which is 100% predictive of confirmed PD leak on ERCP. Furthermore, there have been no retrospective studies that have evaluated a fluid amylase to serum amylase ratio for predicting pancreatic leaks.

Strengths of our study include inclusion of patients with ascites who had confirmed PD leak on ERCP. We also had a control data set with appropriate medical and surgical controls for comparison. Limitations of this study include the retrospective nature and small sample size of the study group. While we did have control groups for comparison, these patients did not have ERCP with pancreatography to demonstrate patent pancreatic ducts, and an assumption was made that the patients did not have pancreatic leaks based on clinical presentation. Another limitation is that we included only patients with ascites, so the generalizability

of the ratio for PD leak other than ascites is limited. Future studies should confirm the efficacy of the ratio in a multi-center retrospective study with a large sample size. Further analysis of the ratio was not performed to predict the clinical course of PD leaks.

In summary, our study revealed that evaluation of the fluid amylase to serum amylase ratio can be used to predict pancreatic leaks. The ratio serves as a noninvasive, diagnostic tool that can aid the clinician in diagnosis and minimizes ERCP as a diagnostic modality, which ultimately reduces the risk of adverse reactions. Patients with an ascitic fluid amylase to serum fluid amylase ratio of at least 6.89 should be considered high risk of having pancreatic duct leaks, and ERCP should be a consideration for management.

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