ORIGINAL ARTICLE

Acute pancreatitis severity according to its etiology: Hypertrigliceridemia *vs.* other causes

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RESUMEN

Antecedentes y propósito del estudio. Evidencia experimental y clínica sugiere que la pancreatitis aguda por hipetrigliceridemia (HIAP) tiene un curso clínico más grave respecto a la pancreatitis por otras causas (POC). El objetivo de este estudio es comparar las características clínicas, complicaciones y desenlaces de los pacientes con HIAP o con POC. **Material y métodos.** Estudio transversal comparativo de pancreatitis agudas (AP) que se presentaron en nuestro hospital durante cuatro años. Se registraron variables clínicas, bioquímicas y de imagen. Se evaluó la gravedad de la PA de acuerdo con escalas pronósticas validadas, se determinó la tasa de ingreso a unidades de cuidados críticos, requerimiento de intubación, complicaciones, estancia hospitalaria y mortalidad. Los datos se analizaron por medio de *t* de Student, χ^2, prueba exacta de Fisher y *U* de Mann Whitney, para comparar al grupo de PHTG con el de POC. **Resultados.** Se incluyeron 21 pacientes con PHTG y 129 con POC. No se observaron diferencias significativas en los índices pronósticos (APACHE II, BISAP, Atlanta, Balthazar e índice de severidad por tomografía) entre los grupos. La tasa de ingreso a unidades de cuidados intensivos fue similar (4.8 *vs.* 5.5%; P = 1.00). El tiempo de estancia hospitalaria no fue estadísticamente diferente (7.7 ± 10 *vs.* 7.3 ± 4.7 días). **Conclusión.** Los pacientes con PHTG presentaron un curso clínico similar a los pacientes con POC. Sin embargo, la información en este sentido aún es insuficiente.

Palabras clave. Pancreatitis. Dislipidemia. Desenlace.

ABSTRACT

Background and purpose of the study. Experimental and clinical evidence suggests that hypertriglyceridemia-induced acute pancreatitis (HIAP) has a more severe clinical evolution compared to pancreatitis due to other causes (POC). The objective of this study is to compare the clinical characteristics, complications, and outcomes of patients with HIAP or POC. **Material and methods.** Transversal comparative study of acute pancreatitis (AP) presented in our hospital for four years. Clinical, biochemical, and imaging variables were recorded. AP severity was assessed according to validated prognostic scales. The rate of admission to critical care units, intubation requirement, complications, inpatient stays, and mortality were recorded. Data were analyzed using the Student's *t*-test, χ^2 test, Fisher exact test, and Mann-Whitney *U* test, to compare the HIAP arm to the POC arm. **Results.** 21 patients with HIAP and 129 patients with POC were enrolled in the study. No significant differences were observed in prognostic indexes (APACHE II, BISAP, Atlanta, Balthazar, and tomography severity index) between both arms. The rate of admission to intensive care units was similar for both (4.8 *vs.* 5.5%; P = 1.00). The length of inpatient stay was not statistically different between such arms (7.7 ± 10 *vs.* 7.3 ± 4.7 days). **Conclusion.** Patients with HIAP exhibited a clinical evolution similar to patients with POC. However, data in this regard are still insufficient.

Key words. Pancreatitis. Dyslipidemia. Outcome.

INTRODUCTION

Acute pancreatitis (AP) means the pancreas inflammation syndrome resulting from an acute injury, followed by a systemic inflammatory response that often does not correspond to the extent of tissue injury.[1] The disease may evolve with a rapid progression and result in severe multiple organ failures.[2] Hypertriglyceridemia-induced acute pancreatitis (HIAP) represents 1 to 4% of AP cases, being only overtaken by acute biliary pancreatitis and pancreatitis resulting from alcohol use.[3]

In addition to hypertriglyceridemia (HTG), there is a second factor that has been proposed for the acceleration of HIAP event,[3,4] such as alcohol,[4] uncontrolled

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Manuscript received: February 27, 2016. Manuscript accepted: March 13, 2016.

diabetes mellitus,[5] pregnancy,[6] drugs such as oral retinoids, diuretics, β-blocking agents, tamoxifen, estrogens, antiretroviral drugs, among others.[4] HTG exacerbated by such second factor starts the damage and results in an early release of pancreatic lipase, which causes a local inflammatory process that later becomes systemic.

The inflammatory response triggered by a vast amount of free fatty acids is believed to be higher than that resulting from AP due to other causes (POC).[7] Animal studies have shown that HTG contributes to the evolution of AP (both edematous and necrotizing), mainly due to lung damage.[7-10] To this respect, the literature has provided contradictory findings, since some studies suggest that HIAP clinical evolution is more severe than for POC[11] and other studies have reported no difference with respect to their prognosis.[3] The aim of this study is to compare clinical characteristics, complications and outcomes among Mexican patients with HIAP versus POC.

MATERIAL AND METHODS

A hospital-based transversal comparative study was performed. It included all AP index events (first event) occurred in the Médica Sur Hospital from January 2007 to May 2011. All of the cases were identified by searching the admission and discharge diagnoses database file of our hospital. All adult patients (over 16 years old) were enrolled if AP diagnosis was confirmed by clinical evidence (abdominal pain suggesting AP), biochemical evidence (lipase and amylase ≥ 3 times the normal upper limit) and/or diagnostic tomography imaging. Patients with index events documented in sites other than this hospital or diagnosed with chronic pancreatitis were excluded.

AP cases were divided in the HIAP arm and the POC arm. In addition to the AP diagnosis, the criteria to determine HIAP included triglyceride levels (TG) ≥ 1,000 mg/dL and exclusion of other AP causes. The criterion to determine POC was AP diagnosed with TG ≤ 1,000 mg/dL at hospital admission. Idiopathic pancreatitis was included in the POC arm, being defined as AP events that could not be diagnosed despite exhaustive medical history, physical examination, laboratory tests, or non-invasive imaging methods such as abdominal ultrasound, computed tomography, magnetic resonance, or endoscopic ultrasound.

Epidemiological, clinical, biochemical, and imaging variables were recorded at each patient's admission. Ranson's criteria within 24 and 48 h,[12] as well as APACHE II,[13] Atlanta,[14] BISAP,[15] Balthazar,[16] and CT se-

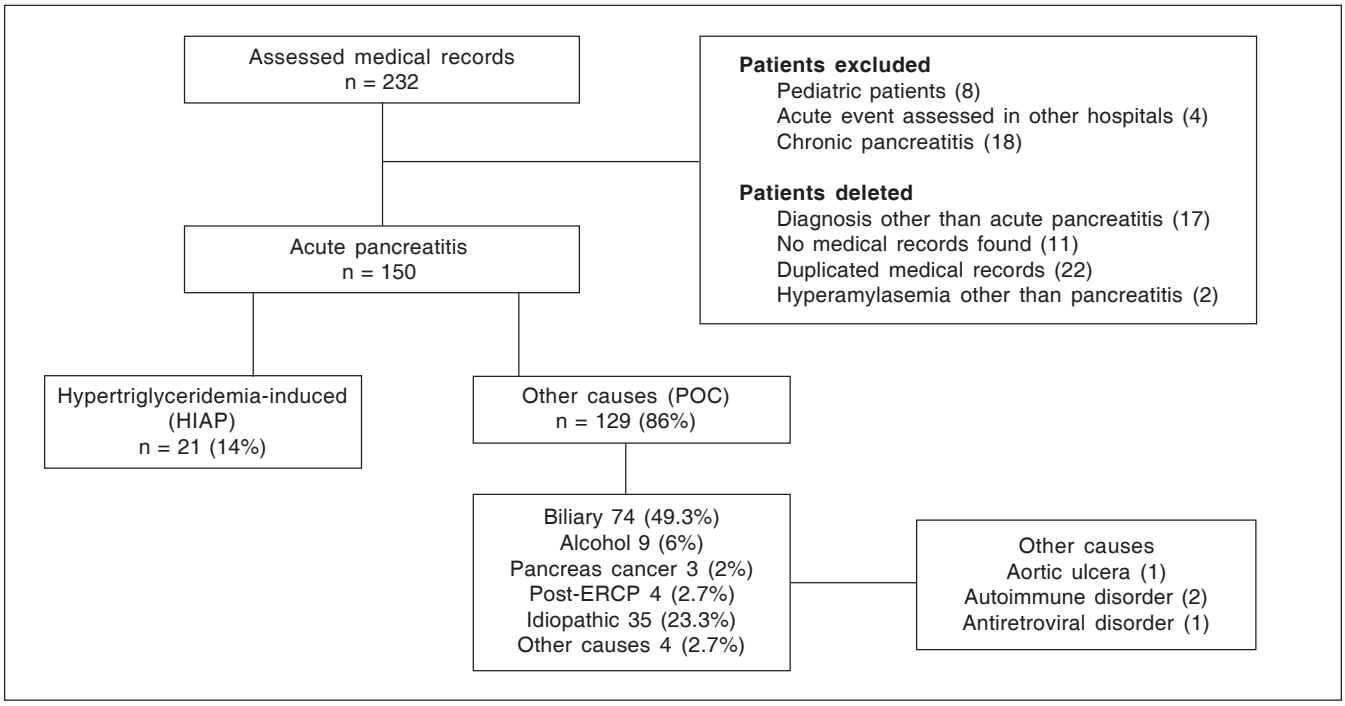

Figure 1. Distribution by groups. ERCP: endoscopic retrograde cholangiopancreatography. HIAP: hypertriglyceridemia-induced acute pancreatitis. POC: pancreatitis due to other causes.[18-22]

verity index (CTSI)[17] were calculated. Severe pancreatitis was determined for patients with APACHE II ≥ 8 points, Ranson's criteria within 24 and 48 h ≥ 3 points or BISAP ≥ 3 points. The following hospital outcomes were documented: Hospital area in which patient was first admitted (Intensive Care Unit [ICU], Secondary Intensive Care Unit (SICU), or hospital general floor), days of inpatient stay in critical care unit, and total days of inpatient stay. The following was also recorded: The need to use invasive mechanical ventilation (IMV) at any time during inpatient stay, the development of pancreatic necrosis, hemor-rhage, or fluid collections. Deaths during inpatient stay, as well as their causes, were also recorded.

Statistical analysis

The SPSS version 19.0 software was used for statistical analysis. Means and standard deviations were used to describe continuous variables and proportions for categorical variables. To assess the differences between categorical variables, a chi-square test or Fisher exact test was carried out. Mean differences in continuous variables were analyzed using the Student's *t*-test and Mann-Whitney *U*

Table 1. Baseline characteristics of patients with acute pancreatitis based on their etiology.

Variable	HIAP (n = 21) mean ± SD	POC (n = 129) mean ± SD	P
Age (years)	42 ± 11	52 ± 18	0.01
Men*	12 (57%)	75 (58%)	0.93
Body mass index (kg/m^2)	27 ± 3.6	27 ± 5	0.91
Systolic blood pressure (mmHg)	132 ± 21	131 ± 21	0.79
Diastolic blood pressure (mmHg)	75 ± 19	77 ± 14	0.72
Mean blood pressure (mmHg)	95 ± 18	95 ± 14	0.91
Temperature (°C)	36.48 ± 0.45	36.47 ± 0.58	0.75
Oxygen saturation (%)	94.95 ± 2.37	94.54 ± 4.13	0.65
Diabetes mellitus type 2*	5 (23.8%)	14 (10.9%)	0.14
Hypertension*	5 (23.8%)	30 (23.3%)	1.00
Dyslipidemia*	8 (38%)	24 (18.6%)	0.04
Alcohol use*	15 (71.4%)	68 (53.1%)	0.11
Estrogens*	2 (9.5%)	2 (1.6%)	0.09
Previous cholecystectomy*	3 (14.3%)	20 (15.5%)	1.00
Hemoglobin (g/dL)	14.78 ± 1.46	15.17 ± 2.06	0.405
Hematocrit (%)	42.96 ± 4.08	44.90 ± 5.79	0.153
Platelets (cells/µL)	233762 ± 75479	238390 ± 71036	0.785
Leucocytes (cells/uL)	13424 ± 3038	12530 ± 4702	0.795
Sodium (mmol/L)	134 ± 7.65	137 ± 4.01	0.001
Potassium (mmol/L)	3.66 ± 0.45	3.92 ± 0.55	0.041
Calcium (mg/dL)	8.02 ± 0.48	10.48 ± 12.15	0.625
Glucose (mg/dL)	217 ± 103	138 ± 44	0.001
Ureic Nitrogen (mg/dL)	11.92 ± 3.67	14.60 ± 7.83	0.136
Creatinine (mg/dL)	0.63 ± 0.27	0.86 ± 0.31	0.003
Triglycerides (mg/dL)	3305 ± 2436	178 ± 134	< 0.001
Cholesterol (mg/dL)	437 ± 219	183 ± 48	< 0.001
HDL cholesterol (mg/dL)	29 ± 10	42 ± 14	0.716
LDL cholesterol (mg/dL)[a]	64 ± 18	107 ± 42	0.083
Total bilirubin (mg/dL)	1.16 ± 0.50	2.27 ± 2.13	0.026
Direct bilirubin (mg/dL)	0.21 ± 0.11	1.12 ± 1.15	0.009
Alanine aminotransferase (U/L)	48 ± 42	178 ± 272	0.035
Aspartate aminotransferase (U/L)	39 ± 20	182 ± 276	0.022
Alkaline phosphatase (U/L)	89 ± 40	139 ± 108	0.045
Gamma-glutamyl transpeptidase (U/L)	141 ± 142	263 ± 308	0.092
Lactate dehydrogenase (U/L)	223 ± 155	309 ± 279	0.218
Albumin (mg/dL)	3.63 ± 0.44	3.70 ± 0.49	0.573
Amylase (U/L)	450 ± 430	1785 ± 1512	0.002
Lipase (U/L)	706 ± 723	1972 ± 2282	0.013

[a] Friedewald formula to estimate: LDL Cholesterol = total cholesterol - [cholesterol - HDL + (TG/5)]. * n(%).

test in variables with non-normal distribution. The correlation of TG levels and prognostic factors was analyzed using lineal regression. A univariate logistic regression analysis was performed to identify prognostic indexes associated with stays in intensive care unit. A P-value of < 0.05 was considered to be statistically significant.

RESULTS

232 patients were assessed, of which 150 had a confirmed diagnosis of AP. They were classified as follows: 21(14%) with HIAP and 129 (86%) with POC. The following were the causes for POC: biliary (n = 74, 49.3%), idiopathic (n = 35, 23.3%), alcohol (n = 9, 6%), post-endoscopic retrograde cholangiopancreatography (n = 4, 2.7%), pancreas cancer (n = 3, 2%), and other causes (n = 4, 2.7%) (Figure 1).

The POC arm was analyzed excluding patients with any kind of dyslipidemia. Nevertheless, no differences were observed in severity indicators, days of inpatient stays, admission to the Intensive Care Unit, or complications (data not shown).

Baseline characteristics for the relevant arms are described in table 1. The HIAP arm was younger in age (42 ± 11 *vs*. 52 ± 18 years, P < 0.01). Concerning comorbidities, a greater proportion of patients with dyslipidemia was observed in the HIAP arm (38 *vs*. 19%, P < 0.04), as well as higher levels of TG (3,305 ± 2,436 *vs*. 178 ± 134 mg/dL, P < 0.001) and cholesterol (437 ± 219 *vs*. 183 ± 48 mg/dL, P < 0.001).

In liver function tests, bilirubin levels were higher in patients with POC (total bilirubin 1.16 ± 0.5 *vs*. 2.27 ± 2.13 mg/dL, P = 0.02; direct bilirubin 0.21 ± 0.11 *vs*. 1.12 ± 1.15 mg/dL, P = 0.009; ALT 48 ± 41 *vs*. 177 ± 247 U/L, P = 0.035; AST 39 ± 20 *vs*. 182 ± 276 U/L, P = 0.022; and alkaline phosphatase 89 ± 40 *vs*. 139 ± 108 U/L, P = 0.04). Levels of amylase (450 ± 430 *vs*. 1785 ± 1512 U/L, P = 0.002) and lipase (706 ± 723 *vs*. 1972 ± 2281 U/L, P = 0.013) were significantly lower in the HIAP arm compared to POC. Finally, glucose levels were higher in patients with HIAP (217 ± 103 *vs*. 138 ± 44 mg/dL, P < 0.001) (Table 1).

AP severity indexes, such as APACHE II, Ranson's criteria within 24 and 48 h, BISAP, Atlanta, Balthazar, and CTSI, did not show differences in individual scores for patients with HIAP or POC (Table 2). Event severity was no different between HIAP or POC groups (Table 2).

The presence of local and systemic complications did not vary between patients with HIAP or POC. There was no difference either in intubation requirements, formation of intra-abdominal fluid collections, hemorrhage, or necrosis. Only one patient died in the POC arm (Table 3).

When assessing the hospital area in which admission occurred after the first evaluation in the Emergency Room, no difference was found between the number of patients admitted in ICU (14.3% *vs*. 7.8, P = 0.396) and SICU (19 *vs*. 14.1%, P = 0.517). There were no differences in the number of transfers from floor beds to ICU beds (4.8% *vs*. 5.5%, P = 1.00) or SICU beds (14.3 *vs*. 7.8%, P = 0.396), in HIAP and POC arms respectively.

Factors associated with inpatient stay in ICU or SICU were also analyzed, with the following being detected as risk factors: presence of APACHE II ≥ 8 points (OR 3.5, IC95% 1.6-7.5, P = 0.002), Ranson's criteria within 48 h ≥ 3

Table 2. Severity scales and criteria in pancreatitis.

Score	HIAP (n = 21)	POC (n = 129)	P
Admission			
APACHE II	4 (0-21)	6 (0-20)	0.444
Ranson's criteria within 24 h	1 (0-2)	1 (0-3)	0.235
Ranson's criteria within 48 h	2 (0-6)	2 (0-8)	0.179
BISAP	2 (0-4)	1 (0-5)	0.747
Atlanta	1 (0-3)	1 (0-4)	0.757
Balthazar	2 (1-4)	2 (0-4)	0.098
CTSI	2 (1-4)	2 (0-6)	0.027
Event Severity			
APACHE II (≥ 8 points)	4 (19%)	39 (30.2%)	0.435
Ranson's criteria within 24h (≥ 3 points)	0 (0%)	11 (8.5)	0.364
Ranson's criteria within 48h (≥ 3 points)	10 (47.6%)	47 (36.4)	0.327
BISAP (≥ 3 points)	0 (0%)	1 (0.8%)	0.999

APACHE II: acute physiology and chronic health evaluation. BISAP: bedside index for severity in acute pancreatitis. HIAP: hypertriglyceridemia-induced acute pancreatitis. POC: pancreatitis due to other causes.

Table 3. Local and systemic complications in acute pancreatitis.

Variable	HIAP (n = 21)	POC (n = 129)	P
Intubation requirement	2 (9.5%)	7 (5.4%)	0.614
Fluid collections	3 (14.3%)	14 (10.9%)	0.709
Hemorrhage	0 (0%)	2 (1.6%)	0.999
Necrosis	1 (4.8%)	3 (2.3%)	0.457
Mortality	0 (0%)	1 (0.8%)	-

HIAP: hypertriglyceridemia-Induced acute pancreatitis. POC: pancreatitis due to other causes.

Table 4. Factors associated to inpatient stay in Secondary Intensive Care Unit or Intensive Care Unit in patients with acute pancreatitis.

Variable	OR (IC95%)	P value
APACHE II (≥ 8 points)	3.5 (1.6-7.5)	0.002
Ranson's criteria within 48h (≥ 3 points)	4.1 (1.3-12.7)	0.023
Atlanta (> 1 point)	5.8 (2.4-14.3)	0.001
Hypertriglyceridemia-induced pancreatitis	1.3 (0.5-3.7)	0.599

Table 5. Length of inpatient stay.

Days of inpatient stay	HIAP (n = 21)	POC(n = 129)	P value
Intensive Care Unit	1.2 ± 7	1.1 ± 2.4	0.397
Secondary Intensive Care Unit	1.8 ± 5.1	2.24 ± 4.5	0.466
Total days of inpatient stay	7.7 ± 10.7	7.3 ± 4.7	0.889

HIAP: hypertriglyceridemia-induced acute pancreatitis. POC: pancreatitis due to other causes.

points (OR 4.1, IC95% 1.3-12.7, P = 0.023), Atlanta > 1 point (OR 5.8, IC95% 2.4-14.3, P = 0.001) (Table 4).

A lineal regression analysis was performed between triglyceride levels and the APACHE II score. No significant cor-relation was observed (r = 0.083, P = 0.317). Furthermore, average TG values according to severity by APACHE II were analyzed and no differences were found between the arms (995 ± 1774 *vs.* 1127 ± 2539 mg/dL, P = 0.687).

Regarding the length of inpatient stay, no significant dif-ference was found between HIAP and POC, with an inpatient stay in ICU of 1.2 ± 7 *vs.* 1.1 ± 2.4 days, an inpatient stay in SICU of 1.8 ± 5.1 *vs.* 2.24 ± 4.5 days, and a total inpatient stay of 7.7 ± 10.7 *vs.* 7.3 ± 4.7 days (Table 5).

DISCUSSION

In this study we observed no difference in the clinical characteristics, evolution or hospital-based prognosis or outcomes of patients with HIAP compared to POC.

We observed too that severity indexes for patients with HIAP are similar to those of patients with POC.

In the epidemiological analysis, the lower age of the patients with HIAP is worth to be noted. This may be associated to the natural history of primary lipoprotein metabolism disorders (primary dyslipidemias), as these disorders frequently manifests in the youth. It is also noteworthy that, in spite of being younger, patients with HIAP exhibit the same evolution and prognosis as older patients with POC and, a priori, this make the former have a worse prognosis. This analysis makes us question ourselves whether the severity in young patients with HIAT is higher but better tolerated due to the young age and good immune condition of such patients. Further studies involving a larger number of patients are needed to analyze age and immune status of patients, to determine whether AP in young patients with HIAT is more severe.

No difference was observed in the prevalence of diabetes, hypertension, dyslipidemia, alcohol use or estrogen use as a trigger for HIAT. This may be due to small sample size.

No differences were observed in the values for high-density and low-density lipoproteins in both groups. We must consider that LDL values are usually not valid in

patients with HTG, due to the usual laboratory estimation of LDL using Friederwald formula. An error grater to 10% (suprastimation) is found in LDL values particularly when triglycerides are grater to 400 mg/dL. As a result, in the HIAT group, LDL values are not trustable (All of the patients had triglycerides grater the 400 mg/dL). The most common dyslipidemia found in the AP population is hypertriglyceridemia and hypoalphalipoproteinemia, which agrees with what has been published before in our country population.[23]

Values for amylase and lipase were lower in patients with HIAP. Regarding this finding, Navarro and colleagues have described lower levels of amylase and lipase in patients with HTG, advancing the hypothesis of a probable interference of lipids with the study, or the presence of a plasmatic and urinary inhibitor with respect to the test, although lipase may probably show better sensitivity and specificity values in these patients.[24] In spite of such difference, it must be remembered that amylase and lipase levels are not correlated to pancreatitis severity or to the development of local or systemic complications.[25]

Differences were found in sodium levels, which was an expected finding already been reported before, due to pseudohyponatremia associated with high triglyceride levels.[26]

Concerning AP severity using severity indexes (APACHE II, Baltazar, Atlanta, etc.), no difference was found between both arms, which confirms what Navarro, *et al*. have reported.[11] However, the results obtained are different from other series, which show a higher frequency of respiratory failure associated to HTG, without influencing the rate of patients requiring intubation.[6,27]

Unlike the study by Navarro, *et al*.,[11] we did not detect a large number of complications such as necrosis, abscesses or death in the HIAP arm. Such differences may be due to the particular characteristics of the arms and populations under study.

Regarding mortality, only one case of death was documented in the POC arm. It was thus not possible to find any significant difference between both arms. The size of our sample is similar to other series. However, it is insufficient to provide statistical power to a clinical outcome as infrequent as mortality.

Finally, our results support the findings reported by Forston, *et al*. that there is no difference in the severity and frequency of local and systemic complications depending on the AP etiology.[3]

The limitations of our study are those implied to single center transversal comparative studies, including a high incidence of idiopathic AP cases, a small number of HIAT cases, lack of information not registered in the clinical history such as family history of pancreatitis (to identify possible primary dislipidemias or genetic abnormalities affecting pancreatic function as a cause), compared to other studies.[28]

We concluded that the evolution and prognosis of patients with PTHG are similar to those with POC. However, the overall experience is still limited and further prospective multicenter studies on the matter are required to identify if a difference in severity, frequency of complications, need for intubation o worse prognosis is related to AP etiology, particularly in the HIAT group.

ABBREVIATIONS

- **AP:** acute pancreatitis.
- **APACHE II:** acute physiology and chronic health evaluation II.
- **BISAP:** bedside index for severity in acute pancreatitis.
- **HIAP:** hypertriglyceridemia-induced acute pancreatitis.
- **ICU:** Intensive Care Unit.
- **POC:** pancreatitis due to other causes.
- **SICU:** Secondary Intensive Care Unit.
- **TG:** triglycerides.

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