BRIEF COMMUNICATIONS

Analysis of 1060 Cases of Drug-Induced Acute Pancreatitis

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Acute pancreatitis (AP) has a mortality of approximately 3%.[1] Its reported incidence is variable across countries (10 to 100/100,000 inhabitants), and in the United States, AP is a significant cause of acute hospitalization for gastrointestinal disorders.[2] Drug-induced AP (DIAP) is regarded as a rare and mild entity; yet, it is estimated to account for approximately 2% to 5% of AP episodes worldwide.[3,4] Because DIAP has no unique features, rechallenge with the offending drug would be the only way to provide the most robust evidence to confirm the etiology. However, giving back the drug only for understanding the etiology of index AP is ethically unacceptable.[3] Therefore, unsurprisingly, DIAP often remains a speculative diagnosis. A more detailed introduction of DIAP can be found in Supplementary Document 1.

We aimed to systematically search the medical literature, analyze the outcomes of all reported cases of DIAP, and compare them against a general cohort of AP.

Methods

We comprehensively searched the literature for reported cases of proven DIAP and extracted detailed data of each case on both first episodes and rechallenges. We compared DIAP to the large cohort of AP cases collected by the Hungarian Pancreatic Study Group. Details of the methods are in Supplementary Document 1.

Results

As a result of the comprehensive search and selection, we identified and analyzed 1060 eligible patients in 856 reports (details of the articles can be found in Supplementary Document 2).

Epidemiology and Outcome Parameters of the First Episodes of Drug-Induced Acute Pancreatitis

In a large proportion of the 1060 patients, antineoplastic (179 [16.89%]), antibiotic (128 [12.08%]), and anticonvulsant (103 [9.72%]) drugs caused DIAP. A combination of drugs caused 78 (7.36%) of the DIAP episodes (Figure 1A). In approximately half of the 1060 patients, drugs were given to manage the diseases of the gastrointestinal tract (214 [20.19%]) or neurologic (158 [14.91%]) or hematologic (155 [14.62%]) conditions (Figure 1B). The 10 most common drugs resulting in AP are shown in Figure 1C.

Male patients comprised 536 of 1054 patients (50.85%) affected by DIAP (Figure 1D). Interestingly, 228 of 1054 cases (21.63%) were reported in children (aged <18 years), and cases were seen at a younger age than in AP of other common etiologies (Figure 1E). Among the 1060 patients, DIAP was severe in 213 (20.09%), moderately severe in 118 (11.13%), and mild in 729 (68.77%), if the first episodes were analyzed (Figure 1F).

DIAP had a mortality of 90 of 1033 (8.71%) for all severities (Figure 1G). There was a significant difference in the median (interquartile range [IQR]) length of hospitalization (LOH) between mild and moderately severe (7 days [IQR, 4–11.5 days] vs 16 days [IQR, 7–25 days], P .001) and between mild and severe DIAP (7 days [IQR, 4–11.5 days] vs 18 days [IQR, 6.5–42 days], P < .001). There was no difference in the LOH between moderately severe and severe DIAP (Figure 1H).

We found information on rechallenge in 960 of the 1060 patients in our analysis. Epidemiology (indication, sex, and age) and outcome parameters (severity, mortality, and LOH) of the rechallenge episodes of DIAP can be found in Figure 2A–F. The association of the drug categories and primary conditions with the severity and mortality rates of DIAP can be found in Supplementary Document 1 and Supplementary Tables 1 and 2.

Effect of Dose on the Outcome of Drug-Induced Acute Pancreatitis After Rechallenge

In 147 of 241 patients (70.00%), no data were available on the dose for rechallenge. Rechallenge was performed in 49 of 241 patients (20.33%) with the same dose as given in the first DIAP episode. The dose was decreased in 33 patients (13.69%) and was increased in 12 (4.98%) compared with the drug dose given in the first episode. If the same dose was given that provoked first episode, DIAP was severe in 2 of 41 patients (4.88%), moderate in 3 (7.32%), and mild in 36 (87.80%). If decreased doses were given, we found no moderately severe cases. Rechallenge in 28 patients caused 1 (3.57%) severe case and 27 (96.43%) mild cases of DIAP (Figure 2G).

Most current article
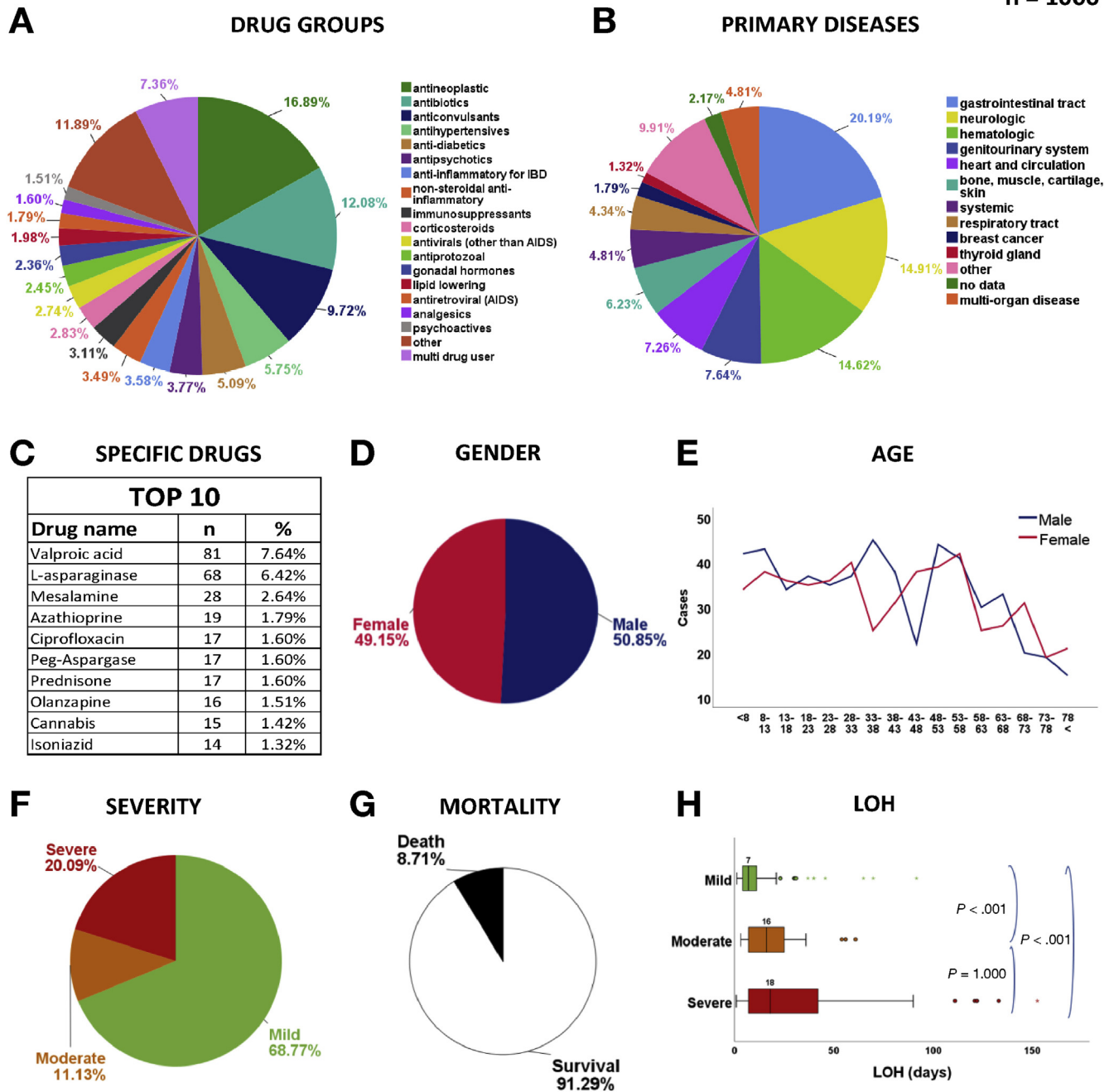
Figure 1. Epidemiology and outcome parameters of the first episodes of DIAP in 1060 patients. (A) Culprit drugs reported are subgrouped according to their mechanism of action. IBD, inflammatory bowel disease. (B) Primary diseases that were the reason for the drug intake are subgrouped according to the affected organ. (C) The top 10 culprit drugs. (D) Sex ratio of patients. (E) Age distribution of patients. (F) Rate of the severities of cases. (G) Mortality. (H) LOH in the 3 different severities. The *horizontal line* in the middle of each box indicates the median; the *top and bottom borders* of the box mark the 75th and 25th percentiles, respectively; the *whiskers* mark the minimum and maximum of all of the data; and the *circles* indicate outliers.

Analysis of Drug-Induced Acute Pancreatitis Versus the General Acute Pancreatitis Cohort

The descriptive statistics of the general AP cohort are available in Supplementary Document 1 and Supplementary Figure 1. Our data showed that severity and mortality were increased in all DIAP cases compared with AP of other etiologies by 18.41% vs 5.63% (*P* < .001) and 7.30% vs 2.20% (*P* <

.001), respectively. DIAP had the second highest mortality rate of all etiologies (8.49%) (Supplementary Document 1 and Supplementary Figure 1).

Discussion

One of the most critical findings of our study is that compared with AP of other etiologies, reported patients
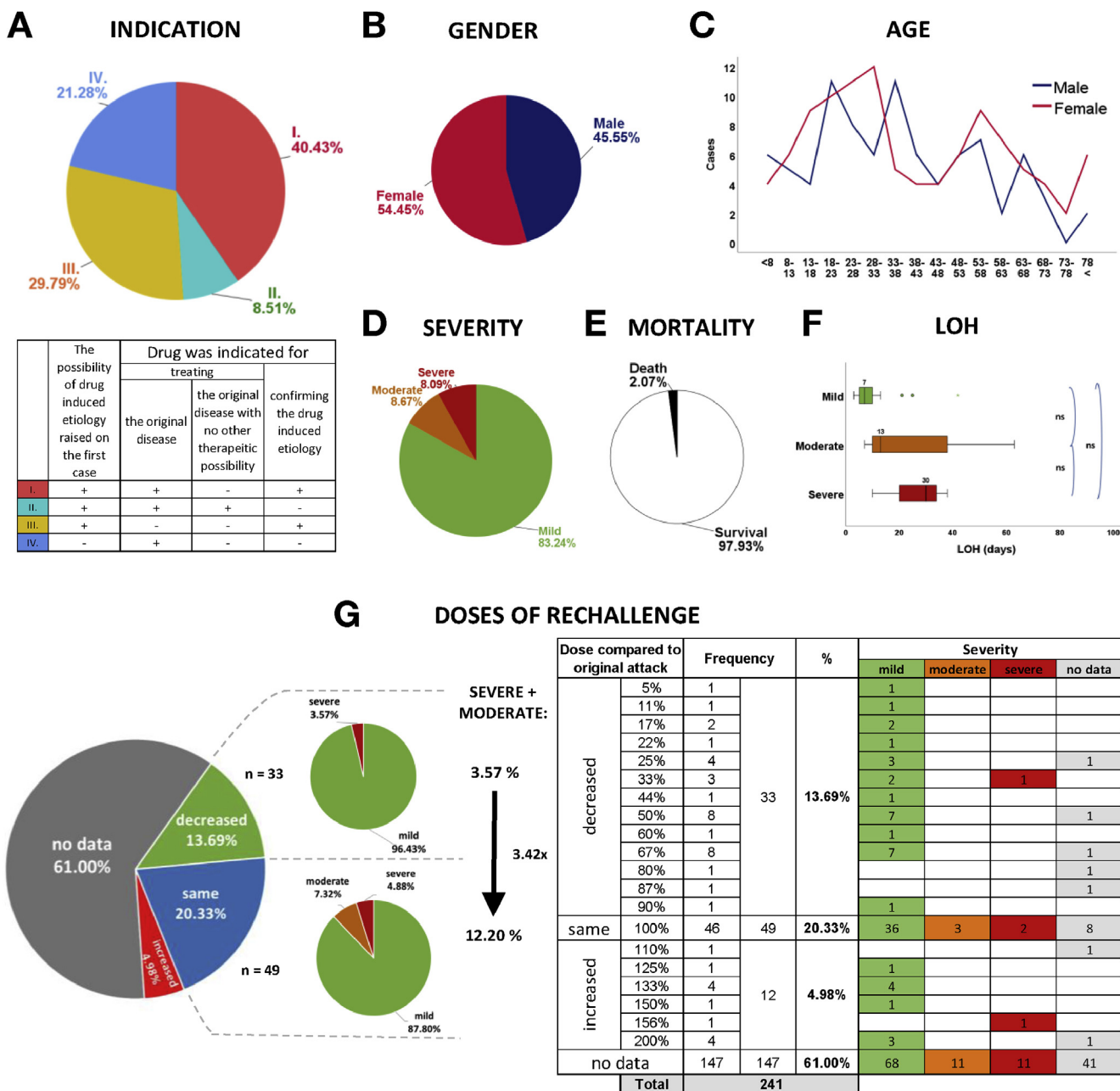
n = 241

Figure 2 (A) INDICATION

	The possibility of drug induced etiology raised on the first case	Drug was indicated for treating		
		the original disease	the original disease with no other therapeutic possibility	confirming the drug induced etiology
I.	+	+	−	+
II.	+	+	+	−
III.	+	−	−	+
IV.	−	+	−	−

DOSES OF RECHALLENGE (G)

Dose compared to original attack		Frequency		%	Severity			
					mild	moderate	severe	no data
decreased	5%	1			1			
	11%	1			1			
	17%	2			2			
	22%	1			1			
	25%	4			3			1
	33%	3			2		1	
	44%	1			1			
	50%	8	33	13.69%	7			1
	60%	1			1			
	67%	8			7			1
	80%	1						1
	87%	1						1
	90%	1			1			
same	100%	46	49	20.33%	36	3	2	8
increased	110%	1						1
	125%	1			1			
	133%	4	12	4.98%	4			
	150%	1			1			
	156%	1					1	
	200%	4			3			1
no data		147	147	61.00%	68	11	11	41
Total			241					

Figure 2. Characterization of rechallenge events in 241 patients. (*A*) Reason for the rechallenge. (*B*) Sex distribution of patients. (*C*) Age distribution of patients. (*D*) Severities of patients. (*E*) Mortality. (*F*) LOH in the 3 severities (ns, no significant difference). The *horizontal line* in the middle of each box indicates the median; the *top and bottom borders* of the box mark the 75th and 25th percentiles, respectively; the *whiskers* mark the minimum and maximum of all of the data; and the *circles* indicate outliers. (*G*) Correlation of drug doses and severity of DIAP in rechallenge. If the drug dose was the same during a rechallenge, the rate of moderately severe and moderate AP cases was 3.42 times more frequent compared with the cases where rechallenge was performed with decreased doses.

with DIAP have a more severe disease course. Most medications causing severe DIAP are given to treat significant preexisting pathologies and primary diseases such as cancers and autoimmune disorders. These patients will have a higher risk of organ failure. In some patients, organ failure is present at the introduction of the offending drug, before the DIAP event. We hypothesize that this accounts for the increased proportion of moderately severe and severe cases of AP in the DIAP cohort.

A primary disease itself is a comorbidity and often has other comorbidities. We believe that the more severe the primary disease was, the higher doses of the offending

drugs were used, leading to more severe courses of the DIAP patients. The offending drugs likely cause the DIAP in a dose-dependent way.

In our recent meta-analysis, older age led to a more severe disease course,[5] and our recent cohort analysis proved that comorbidities are more critical in AP than age.[6] These conclusions are in line with the findings of the present study and support our above-detailed hypothesis.

Besides the negative effect of comorbidities on the outcome of pancreatitis, culprit drugs have direct toxic effects on acinar cells as well. Asparaginase, for example, was shown to cause cellular necrosis.[7] Importantly, here we report for the first time that when rechallenge was done with a decreased dose of the offending drug, it resulted in less severe outcomes. The main strength and limitations of this study are in Supplementary Document 1.

Here we conclude that reported cases of DIAP have worse outcomes than AP of other etiologies and seem to be dose-dependent. If rechallenge is necessary, we recommend that patients are closely monitored and receive a reduced drug dose. Evidence-based guidelines on DIAP and rechallenge should be developed.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.07.016.

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Appendix
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Supplementary Material

Drug-induced acute pancreatitis (DIAP) is regarded as a rare entity; yet, it is estimated to account for approximately 2% to 5% of acute pancreatitis (AP) episodes worldwide.[1–5] However, estimates vary due to the challenging diagnosis and the difficulties of causality assessment.[6–8] Because DIAP has no unique features that would help in distinguishing a case of DIAP from other etiologies, a rechallenge with the offending drug resulting a relapse of DIAP still means the most reliable evidence in confirming the etiology.[3,9] In most cases, intentional rechallenge is considered unethical due to the potentially life-threatening complications of AP; therefore, DIAP remains a speculative diagnosis of exclusion.

The subject of past reviews is usually the categorization of the drugs based on their reported frequency of provoking DIAP[4,10] and the analysis of the strength of the causal relationship between the drug intake and the AP episode.[11–13] According to the literature, most cases of DIAP are mild, self-limited, and dose-independent, with a rapid resolution upon discontinuation of the offending drug.[14] However, in our previous study on 5-aminosalicylic acid–induced DIAP, we found that DIAP might not be dose-independent, and we saw more moderately severe cases than expected.[15]

Methods

Systematic Search

We performed a systematic literature search according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[16] The review was registered on PROSPERO under the ID number CRD42017079196. The following PECO items were used: P = patients with AP; E = DIAP; C = AP caused by other etiologies; and O = severity, mortality, length of hospitalization (LOH), imaging alterations, symptoms, and time to resolution of AP. The search was performed in May 2019 on PubMed, EMBASE, and Cochrane Library with the search terms "acute pancreatitis" and "drug" and was limited to English-language and human studies (if applicable), regardless of the date of publication. Study selection was performed in parallel by 2 independent researchers. Studies that contained pooled statistical data of DIAP were excluded because they did not provide relevant data for our analysis.

Inclusion and Exclusion Criteria

Records that contained relevant data on patients with DIAP were eligible for our study irrespective of study design (case reports included as well). Cases reported as DIAP in which alcoholic or gallstone or different obvious etiology could be suspected were not included.

Risk of Bias

We developed an assessment tool for the reporting quality of the identified articles to exclude poorly reported cases, which would threaten data quality and the analysis.

We identified 3 categories of reporting quality, based on the reported symptoms and signs of AP (abdominal pain, pancreatic enzyme elevation, imaging changes) and their causality with the offending drug.

Strong evidence: The report contained data sufficient to reevaluate the event as DIAP.

Moderate evidence: The report described the event as DIAP, but data only partially confirmed it (could not be reevaluated as AP).

Weak evidence: The report described the event as DIAP, but there was no detailed data for reevaluation.

In our analysis, we included in the statistical analysis only cases with strong evidence levels.

Definition of Acute Pancreatitis

We reevaluated all events documented by the authors as AP. Each was considered as AP if it met the criteria detailed in the evidence-based guidelines for the management of AP.[17,18]

To assess severity, any organ failure reported by the authors was accepted, even if there were no supporting data. Persistent organ failure was defined that lasted longer than 48 hours or was described as persistent by the original authors themselves, transient organ failure was defined that resolved within 48 hours, or described as transient by the authors.

We accepted the pancreatic enzyme level elevation as higher than triple the upper limit of normal if (1) the exact enzyme level and the upper limit of normal were described and the enzyme level exceeded more than 3 times, (2) the precise extent of elevation compared with the upper limit of normal was provided and was more than 3-fold, and (3) the exact pancreatic enzyme levels were given without their references but were higher than 300 U/L in the case of amylase and 180 U/L in the case of lipase.

Rechallenge

We considered the result of rechallenge positive if a trial with the suspected offending drug resulted in the increase of the pancreatic enzyme levels, with or without abdominal pain, nausea, or vomiting.

Severity of Drug-Induced Acute Pancreatitis

To determine the severity of DIAP, we performed an evaluation using the data provided by the authors. We screened each case for the description of local and systemic complications and organ failure. If the detailed clinical data were available, the severity of DIAP was determined by the modified Atlanta criteria, irrespective of the classification by the original authors. If the lack of clinical data did not allow us to determine the severity of DIAP, we used the severity grade reported by the authors.

Primary Disease and Drug Categorization

The offending drugs were given to manage specific disorders. We defined these as the primary diseases.

Acute Pancreatitis Cohort

For the comparative statistical analysis of the DIAP cases to analyze them against AP of other etiologies, we used the detailed clinical data of the AP cohort of the Hungarian Pancreatic Study Group, as described in our previous studies[19–22]

Interpretation of Data

We used descriptive statistical tools to characterize the population, and relative frequency and median and interquartile range were calculated. To analyze the differences between the severity groups for the LOH and the time that the enzyme level and symptoms normalized, we applied the Kruskal-Wallis test with the Mann-Whitney U test as a post hoc test. Differences between drug and disease categories and differences for DIAP against other etiologies of AP were examined using the χ^2 test. We regarded a P value of <.05 as statistically significant. The available-case analysis was used for missing data. Statistical analyses were performed using IBM-SPSS for Windows 25 software (IBM Corp, Armonk, NY).

Additional Results

Outcomes of Drug-Induced Acute Pancreatitis Compared With Acute Pancreatitis With Other Etiologies

We compared the severity and mortality rates of DIAP to AP caused by the more common etiologies like biliary diseases, idiopathic etiology, alcohol consumption, lipid metabolism disorder, status after endoscopic retrograde cholangiopancreatography, and the combinations of these. The detailed descriptive statistics of the AP cohort are shown in Supplementary Figure 1.

We found that DIAP showed the most severe episodes if only the first episodes were analyzed (213 of 1060 [20.09%]; Supplementary Figure 1). If the severe cases of first and rechallenged events were pooled, the rate of severe cases was slightly but not significantly lower (227 of 1301 [18.41%]). Significant differences were seen between the rate of severe and mortality rates of DIAP cases if the first episodes are compared with rechallenges, at 20.09% vs 8.09% ($P < .001$) and 8.49% vs 2.07% ($P < .001$), respectively. Severity and mortality were increased in all DIAP compared with cases with all other etiologies, at 18.41% vs 5.63% ($P < .001$) and 7.30% vs. 2.20% ($P < .001$), respectively. DIAP had the second highest mortality rate of all etiologies (8.49%). Only AP of combined alcoholic and biliary etiology had a similarly high mortality rate (8.7%; Supplementary Figure 1).

The Association of the Drug Categories With the Severity and Mortality Rates of Drug-Induced Acute Pancreatitis

Antiprotozoal drugs, corticosteroids, and antiretrovirals were responsible for the most severe cases of DIAP in 12 of 26 patients (46.15%), 13 of 30 (43.33%), and 7 of 19 (36.84%), respectively. Corticosteroids, antiprotozoal drugs, and antiretrovirals had the highest mortality rates, at 12 of 30 patients (40.00%), 8 of 26 (30.77%), and 5 of 19 (26.32%), respectively. Patients who were taking antiprotozoals (46.15%; $P < .01$), corticosteroids (43.33%; $P < .01$), antihypertensives (29.51%; $P < .05$), and antineoplastics (24.58%; $P < .001$) had a higher chance of severe disease than patients taking other drugs. In contrast to this, patients taking antiinflammatory drugs for inflammatory bowel disease (10.53%; $P < .5$), antibiotics (7.03%; $P < .001$), or other drugs than the specified ones (14.29%; $P < .05$) had a lower chance of a severe episode than patients taking other drugs. Patients taking anticonvulsants had a significantly higher chance of moderately severe DIAP (24.27%; $P < .001$) than patients taking other drugs. Patients taking corticosteroids (40.00%; $P < .001$), antiprotozoals (30.77%; $P < .01$), antiretrovirals (26.32%; $P < .05$), antihypertensives (21.31%; $P < .01$), and patients on multiple medications (15.58%; $P < .05$) had a higher chance of mortality than those taking other drugs. However, patients on antibiotics had a smaller chance of mortality than patients taking other drugs (3.15%; $P < .05$; Supplementary Table 1).

The Association of the Primary Conditions With the Severity and Mortality Rates of Drug-Induced Acute Pancreatitis

The severity of DIAP was analyzed for subgroups of primary diseases, which showed that patients with breast cancer, hematologic conditions, and cardiovascular failure had the highest rates of severe DIAP, at 6 of 19 (31.58%), 45 of 155 (29.03%), and 20 of 77 (25.97%), respectively. Underlying gastrointestinal tract disease had a lower chance of severe DIAP (12.15%; $P < .001$) than other diseases. Hematologic disorders had a higher rate of a severe DIAP episode (29.03%; $P < .001$) than in other conditions. Neurologic conditions had a significantly higher chance for a moderately severe DIAP (20.89%; $P < .001$) than in other diseases. Mortality was lower among patients with gastrointestinal tract disease (3.38%; $P < .01$) and higher in multiple diseases (19.61%; $P < .05$), heart and circulatory diseases (19.48%; $P < .001$), and systemic diseases (17.65%; $P < .05$) than in other diseases (Supplementary Table 2).

Strengths

To our knowledge, this is the only study that comprehensively searched and identified all DIAP cases in the literature. We followed a rigorous methodology, including data extraction and quality analysis of each individual article, to generate an extensive database of reported cases of DIAP. We used this broad database to analyze the natural history of DIAP. Our systematic and comprehensive search identified and resulted in a very detailed data of 1060 cases of DIAP. To date, this is the largest and most comprehensive analysis of all reported cases of DIAP. Because we collected data on the first episodes of DIAP and on rechallenges, we could compare the 2 entities.

Limitations

This study is based on data extracted from case reports and case series, which introduces all of the limitations of

the genre, most importantly, recall and publication bias.[23] The publication bias was increased by the English language filter, which we had to use due to a large number of records identified by the preliminary search. Case reports and series publications, which are almost always written in retrospect, may contain insufficient data, which is a concern.

The latency period between drug exposure and the start of the pancreatitis episode was not defined, and this is a limitation of our study. Owing to the lack of data, Naranjo's score could not be used,[23] which is another significant limitation of the interpretation of the results.

The definition of DIAP after rechallenge needs careful consideration. The fluctuation of pancreatic enzyme levels and incomplete resolution of morphologic changes after an episode of acute pancreatitis make the clinical assessment of recurrent pancreatitis difficult, following the rechallenge with the suspected drug.

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Supplementary Document 2

Preferred Reporting Items for Systematic Review and Meta-analysis
Details of studies

Supplementary Table 1. The Association of the Drug Categories With the Severity and Mortality Rates of Drug-Induced Acute Pancreatitis

Drug		Frequency	Severity			Mortality		Sex		Age, y					Severity
			Severe	Moderate	Mild	Yes	No	Male	Female	<18	18-30	30-50	50-70	≥70	
Antiprotozoals	n	26	12	2 7.69	12	8	18	18	8	0	13	13	0	0	46.15%
	%	2.45	46.15[a]	7.69	46.15	30.77[a]	69.23	69.23	30.77	0.00	50.00	50.00	0.00	0.00	
Corticosteroids	n	30	13	3	14	12	18	18	12	11	4	6	8	1	
	%	2.83	43.33	10.00	46.67	40.00[b]	60.00	60.00	40.00	36.67	13.30	20.00	26.67	3.33	
Antiretrovirals (AIDS)	n	19	7	3	9	5	14	11	8	3	3	10	3	0	
	%	1.79	36.84	15.79	47.37	26.32[c]	73.68	57.89	42.11	15.79	15.79	52.63	15.79	0.00	
Antipsychotics	n	40	12	6	22	3	37	26	14	2	7	21	6	3	
	%	3.77	30.00	15.00	55.00	7.50	92.50	65.00	35.00	5.13	17.95	53.85	15.38	7.69	
Antihypertensives	n	61	18	1	42	13	48	34	27	0	7	13	33	8	
	%	5.75	29.51[c]	1.64	68.85	21.31[a]	78.69	55.74	44.26	0.00	11.48	21.31	54.10	13.11	
Analgesics (non-NSAIDs)	n	17	5	0	12	1	16	3	14	2	4	6	4	1	
	%	1.60	29.41	0.00	70.59	5.88	94.12	17.65	82.35	11.76	23.53	35.29	23.53	5.88	
Gonadal hormones	n	25	7	3	15	1	24	8	17	0	8	16	1	0	
	%	2.36	28.00	12.00	60.00	4.00	96.00	32.00	68.00	0.00	32.00	64.00	4.00	0.00	
Antidiabetics	n	54	15	6	33	3	51	24	30	0	2	14	28	10	
	%	5.09	27.78	11.11	61.11	5.56	94.44	44.44	55.56	0.00	3.70	25.93	51.85	18.52	
Antineoplastics	n	179	44	35	100	8	147	83	96	86	18	30	37	8	
	%	16.89	24.58[b]	19.55	55.87	5.16	94.84	46.37	53.63	48.04	10.06	16.76	20.67	4.47	
Anticonvulsants	n	103	19	25	59	9	94	61	39	62	15	12	7	5	
	%	9.72	18.45[b]	24.27	57.28	8.74	91.26	61.00	39.00	61.39	14.85	11.88	6.93	4.95	
Immunosuppressants	n	33	4	2	27	0	32	19	13	10	8	6	8	1	
	%	3.11	12.12	6.06	81.82	0.00	100.00	59.38	40.63	30.30	24.24	18.18	24.24	3.03	
NSAIDs	n	37	4	1	32	0	37	15	22	6	5	7	10	9	
	%	3.49	10.81	2.07	86.49	0.00	100.00	40.54	59.46	16.22	13.51	18.92	27.03	24.32	
Anti-inflammatory drugs for IBD	n	38	4	1	33	2	36	16	22	9	12	16	1	0	
	%	3.58	10.53[b]	2.63	86.84	5.26	94.74	42.11	57.89	23.68	31.58	42.11	2.63	0.00	
Antivirals (other than AIDS)	n	29	3	2	24	1	28	17	12	1	3	12	11	2	
	%	2.74	10.34	6.90	82.76	3.45	96.55	58.62	41.38	3.45	10.34	41.38	37.93	6.90	
Lipid-lowering drugs	n	21	2	2	17	2	19	8	13	0	1	3	11	6	
	%	1.98	9.52	9.52	80.95	9.52	90.48	38.10	61.90	0.00	4.78	14.29	52.38	28.57	
Antibiotics	n	128	9	9	110	4	123	58	69	12	28	34	30	22	
	%	12.08	7.03[a]	7.03	85.94	3.15[c]	96.85	45.67	54.33	9.52	22.22	26.98	23.81	17.46	
Psychoactives	n	16	1	2	13	1	15	15	1	1	10	4	0	1	6.25%
	%	1.51	6.25	12.50	81.25	6.25	93.75	93.75	6.25	6.25	62.50	25.00	0.00	6.25	
Other	n	126	18	8	100	5	121	61	64	18	14	37	36	20	
	%	11.89	14.29[b]	6.35	79.37	3.97	96.03	48.80	51.20	14.40	11.20	29.60	28.80	16.00	
On multiple medications	n	78	16	7	55	12	65	41	37	5	13	19	32	9	
	%	7.36	20.51	8.97	70.51	15.58[c]	84.42	52.56	47.44	6.41	16.67	24.36	41.03	11.54	
Total	n	1060	213	118	729	90	943	536	518	228	175	279	266	106	
	%	100.00	20.09	11.13	68.77	8.71	91.29	50.85	49.15	21.63	16.60	26.47	25.24	10.06	

IBD, inflammatory bowel disease; NSAID, non-steroidal anti-inflammatory drug.
[a]$P < .01$.
[b]$P < .001$.
[c]$P < .05$.

Supplementary Table 2. The Association of the Primary Conditions With the Severity and Mortality Rates of Drug-Induced Acute Pancreatitis

Ranking based on severity (organ systems affected by the primary diseases)

Primary condition		Frequency	Severity			Mortality		Sex		Age, y					Severity	
			Severe	Moderate	Mild	Yes	No	Male	Female	<18	18-30	30-50	50-70	≥70		
Breast cancer	n	19	6	3	10	0	19	0	19	0	0	13	6	0		31.58%
	%	1.79	31.58	15.79	52.63	0.00	100.00	0.00	100.00	0.00	0.00	68.42	31.58	0.00		
Hematologic	n	155	45	29	81	15	122	84	71	90	23	22	17	3		
	%	14.62	29.03[a]	18.71	52.26	10.95	89.05	54.19	45.81	58.06	14.84	14.19	10.97	1.94		
Heart and circulation	n	77	20	3	54	15	62	39	38	1	9	14	38	15		
	%	7.26	25.97	3.90	70.13	19.48[a]	80.52	50.65	49.35	1.30	11.69	18.18	49.35	19.48		
Respiratory tract	n	46	10	3	33	5	40	23	23	3	6	14	17	6		
	%	4.34	21.74	6.52	71.74	11.11	88.89	50.00	50.00	6.52	13.04	30.43	36.96	13.04		
Systemic	n	51	11	3	37	9	42	26	25	10	8	13	14	6		
	%	4.81	21.57	5.88	72.55	17.65[b]	82.35	50.98	49.02	19.61	15.69	25.49	27.45	11.76		
Neurologic	n	158	31	33	94	10	148	88	69	62	28	38	20	9		
	%	14.91	19.62[a]	20.89	59.49	6.33	93.67	56.05	43.95	39.49	17.83	24.20	12.74	5.73		
Bone, muscle, cartilage, skin	n	66	11	9	46	3	62	35	30	11	5	12	20	16		
	%	6.23	16.67	13.64	69.70	4.62	95.38	53.85	46.15	17.19	7.81	18.75	31.25	25.00		
Genitourinary system	n	81	13	6	62	7	74	26	54	6	19	33	17	6		
	%	7.64	16.05	7.41	76.54	8.64	91.36	32.50	67.50	7.41	23.46	40.74	20.99	7.41		
Gastrointestinal tract	n	214	26	16	172	7	200	112	101	21	31	52	79	30		
	%	20.19	12.15[a]	7.48	80.37	3.38[c]	96.62	52.58	47.42	9.86	14.55	24.41	37.09	14.08		
Thyroid gland	n	14	1	1	12	0	14	2	12	2	0	4	5	3		7.14%
	%	1.32	7.14	7.14	85.71	0.00	100.00	14.29	85.71	14.29	0.00	28.57	35.17	21.43		
Other	n	105	21	8	76	7	98	59	44	14	27	35	18	9		
	%	9.91	20.00	7.62	72.38	6.67	93.33	57.28	42.72	13.59	26.21	33.98	17.48	8.74		
Multiple diseases	n	51	16	4	31	10	41	31	20	7	14	21	7	2		
	%	4.81	31.37	7.84	60.78	19.61[b]	80.39	60.78	39.22	13.73	27.45	41.18	13.73	3.92		
No data	n	23	2	0	21	2	21	11	12	1	5	8	8	1		
	%	2.17	8.70	0.00	91.30	8.70	91.30	47.83	52.17	4.35	21.74	34.78	34.78	4.35		

Supplementary Table 2. Continued

Primary condition		Frequency	Ranking based on severity (organ systems affected by the primary diseases)												Severity
			Severity			Mortality		Sex		Age, y					
			Severe	Moderate	Mild	Yes	No	Male	Female	<18	18-30	30-50	50-70	≥70	
Total	n	1060	213	118	729	90	943	536	518	228	175	279	266	106	
	%	100	20.09	11.13	68.77	8.71	91.29	50.85	49.15	21.63	16.60	26.47	25.24	10.06	

[a]$P < .001$.
[b]$P < .05$.
[c]$P < .01$.

GENERAL COHORT OF AP

n = 1225

A: GENDER

Female 44.24%

Male 55.76%

B: AGE

C: SEVERITY

Severe 5.63%

Moderate 25.96%

Mild 68.41%

D: MORTALITY

Death 2.20%

Survival 97.80%

E: LOH
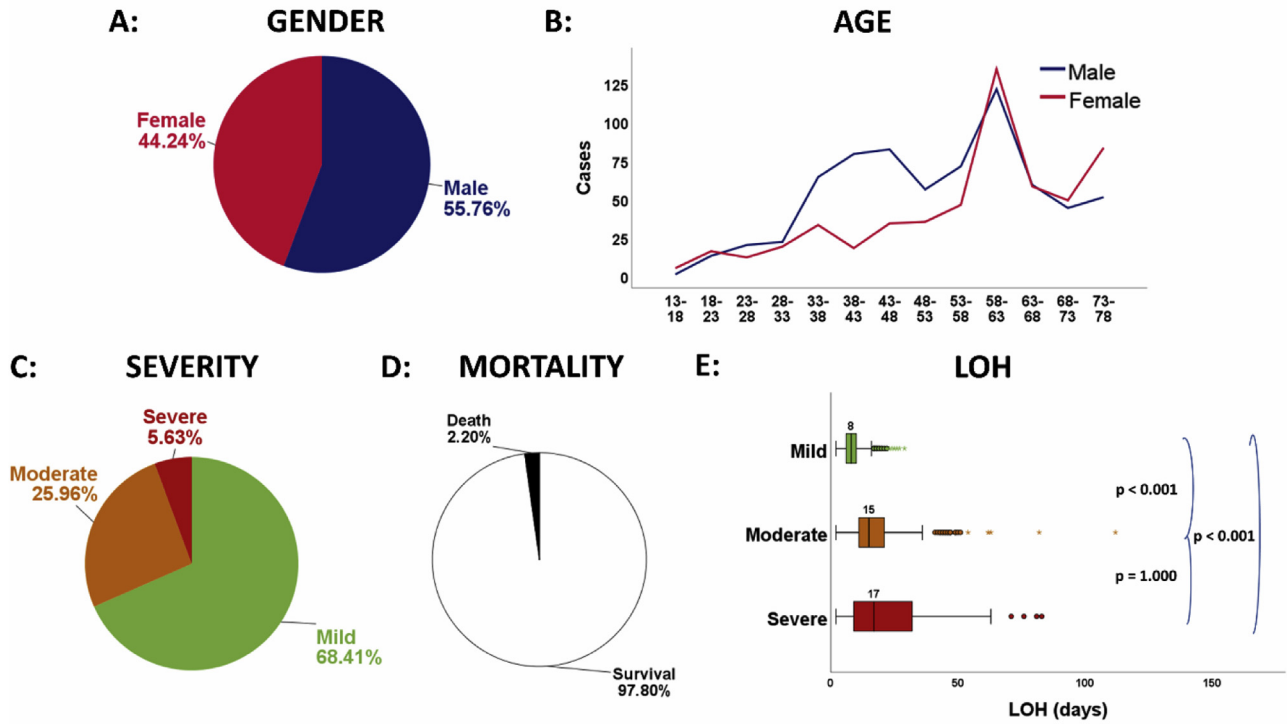
F: DRUG VS. OTHER ETIOLOGIES OF ACUTE PANCREATITIS

	Frequency		Severity						Mortality	
			Mild		Moderate		Severe			
drug induced (first episodes)	1060		729	68.77%	118	11.13%	213	20.09% [a]	90	8.49% [a]
drug induced (rechallenges)	241		144	83.24%	15	8.67%	14	8.09%	5	2.07%
TOTAL (drug induced)	1301		873	70.80%	133	10.79%	227	18.41% [b]	95	7.30% [b]
biliary	471	38.45%	368	78.13%	84	17.83%	19	4.03% [***]	5	1.06% [***]
idiopathic	243	19.84%	157	64.61%	64	26.34%	22	9.05% [***]	9	3.70% [**]
alcoholic	184	15.02%	110	59.78%	68	36.96%	6	3.26% [***]	4	2.17% [**]
lipid metabolic disorder	44	3.59%	20	45.45%	18	40.91%	6	13.64% [***]	0	0.00% [*]
post ERCP	34	2.78%	24	70.59%	10	29.41%	0	0.00% [***]	0	0.00%
others (virus infection, trauma, etc.)	100	8.16%	64	64.00%	30	30.00%	6	6.00% [***]	4	4.00%
alcoholic + biliary	23	1.88%	16	69.57%	6	26.09%	1	4.35% [*]	2	8.70%
alcoholic + lipid metabolic disorder	17	1.39%	8	47.06%	6	35.29%	3	17.65% [*]	0	0.00%
other combination	109	8.90%	71	65.14%	32	29.36%	6	5.50% [***]	3	2.75% [*]
TOTAL (other etiologies)	1225		838	68.41%	318	25.96%	69	5.63%	27	2.20%

Supplementary Figure 1. The general cohort of AP: (*A*) sex ratio, (*B*) age distribution, (*C*) severity of AP, (*D*) mortality, and (*E*) LOH stay (n = number of cases.) The *horizontal line* in the middle of each box indicates the median; the *top and bottom borders* of the box mark the 75th and 25th percentiles, respectively; the *whiskers* mark the minimum and maximum of all of the data; and the circles indicate outliers. (*F*) Severity and mortality rates of DIAP compared with the other etiologies of P. a: drug-induced first episodes vs drug-induced rechallenges, $P < .001$; b: all DIAP vs all AP of other etiologies, $P < .001$; ***$P < .001$; **$P < .01$; *$P < .05$. Further significant differences are marked with stars for other etiology vs first episodes of DIAP. ***$P < .001$, **$P < .01$, *$P < .05$.