Low-enzyme acute pancreatitis—a diagnostic blind spot in current guidelines

We read with great interest the article by Huang *et al*, *'Parecoxib sequential with imrecoxib for occurrence and remission of severe acute pancreatitis'*, recently published in *Gut*.[1]

In this study, acute pancreatitis (AP) was diagnosed based on characteristic symptoms, imaging signs and elevated serum amylase and/or lipase levels.[2] Although these biochemical markers are integral to current international guidelines,[3] a subset of patients not meeting the diagnostic enzyme elevation criterion may be excluded, thereby underestimating disease burden and potentially overestimating the effectiveness of a therapy in these groups.

Previous experimental studies have shown that pancreatic enzyme synthesis can be altered in both AP and diabetes, potentially affecting acinar cell function. For instance, while low-dose cholecystokinin-8 promotes pancreatic regeneration after injury in normal rats, this regenerative response is blunted in diabetic models, accompanied by aggravated cellular and endocrine damage.[4]

Based on these previous findings, we aimed to investigate diabetes as a potential risk factor and to identify further risk factors for enzyme levels that do not meet diagnostic criteria in an AP population.

We analysed data from 4162 AP patients from 14 countries and 29 centres enrolled in the international prospective Acute Pancreatitis Registry of the Hungarian Pancreatic Study Group between 2014 and 2023.[5] On admission, amylase and lipase levels as well as potential risk factors for lower enzyme levels were investigated. Further details of the methodology and the general characteristics of the cohort can be found in the online supplementary methods description and online supplemental tables 1-3 and 5.

We found that diabetic patients showed significantly lower mean pancreatic enzyme levels compared with non-diabetic patients (amylase: 834 (±921) U/L vs 1018 (±1145) U/L, p<0.0001; lipase: 2161 (±2944) U/L vs 2415 (±3134) U/L, p=0.0239) (online supplemental figure 1). Diabetes was significantly associated with non-diagnostic serum amylase (OR=1.34, 95% CI 1.12 to 1.60, p=0.001) and serum lipase levels (OR=1.35, 95% CI: 1.03 to 1.77, p=0.029) at admission. Furthermore, using a machine learning model, we found that smoking, having diabetes at admission, alcohol-induced aetiology or chronic pancreatitis (CP) are associated with lower enzyme levels (online supplemental figures 2–4).

Table 1 Independent risk factors of pancreatic enzyme levels not reaching the diagnostic criterion

Variable	N	Event N	OR	95% CI	P value
Sex	3723	243			
Female	1619	79	1.000	—	
Male	2104	164	1.220	0.902 to 1.650	0.201
Age	3723	243	0.996	0.987 to 1.000	0.341
BMI	3723	243	1.010	0.991 to 1.040	0.235
Diabetes mellitus	3723	243			
No	2822	160	1.000	—	
Yes	**901**	**83**	**1.500**	**1.100 to 2.040**	**0.011**
Chronic pancreatitis	3723	243			
No	3323	197	1.000	—	
Yes	**400**	**46**	**1.640**	**1.120 to 2.350**	**0.009**
Aetiology	3723	243			
Idiopathic	817	63	1.000	—	
Alcohol	751	59	0.944	0.636 to 1.400	0.776
Alcohol-HTG	91	11	1.500	0.712 to 2.910	0.256
Biliary	1590	**58**	**0.499**	**0.340 to 0.730**	**<0.001**
HTG	130	18	1.450	0.782 to 2.580	0.221
Other	344	34	1.230	0.781 to 1.900	0.363

Dependent variable: no diagnostic enzyme elevation (amylase<300 U/L, lipase<180 U/L), Reference: diagnostic enzyme elevation. ORs were derived from a multivariable logistic regression model mutually adjusted for all variables listed. Event N, the number of patients whose outcome was the absence of diagnostic enzyme elevation.; HTG, hypertriglyceridaemia; N, number of patients with available data for each variable.

Importantly, in our cohort, 268 patients (6.7%) were diagnosed with AP based solely on imaging findings and abdominal pain, without meeting the criterion of elevated serum pancreatic enzyme levels. Compared with patients with diagnostic serum enzyme elevation, those without diagnostic enzymes had a higher prevalence of diabetes (33.2% vs 23.7%, p<0.001), smoking (44.1% vs 35.0%, p=0.003) and CP (18.3% vs 10.0%, p<0.001) (online supplemental table 4).

In a multivariable logistic regression model, diabetes and CP remained independently associated with pancreatic enzyme levels that did not meet the AP diagnostic criterion (table 1).

These findings illustrate how easily misdiagnosis may occur in this population, particularly when ultrasound imaging reports that the pancreas cannot be assessed due to overlying bowel gas.

Moreover, in the cohort analysis of Párniczky *et al*, a large proportion of patients (40.5%) was diagnosed without imaging signs or abdominal pain, suggesting that even more cases are likely to be missed in the absence of diagnostic enzyme elevation.[6]

Our findings indicate that relying on the current diagnostic serum enzyme elevation criterion may overlook parts of the clinical spectrum of AP, especially in patients with metabolic or structural pancreatic impairment. Further studies are needed to assess the extent of underdiagnosis and to reconsider serum enzyme thresholds in these specific subpopulations. In patients with risk factors for lower enzyme levels, extended evaluation may reduce missed diagnoses. This limitation could also be considered in clinical trial designs, where refined inclusion criteria could improve representativeness[7] and enhance the generalisability of results.

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