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Research Article

Clinical and laboratory correlates of low fecal elastase-1 levels: A retrospective analysis

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Abstract

Objectives: Fecal elastase-1 (FE-1) is widely used as a noninvasive, stool-based test to evaluate pancreatic exocrine function. This study compared radiological and laboratory findings between patients with low and normal FE-1 levels and investigated variables independently associated with low FE-1 levels.

Methods: The records of 1,133 patients who underwent FE-1 testing were retrospectively reviewed. Patients were classified into normal (≥200 µg/g, n=961) and low (<200 µg/g, n=172) FE-1 groups. Group comparisons and multivariable logistic regression analyses were performed. To assess the incremental discriminative contribution of pancreatic amylase while avoiding confounding due to differences in sample size, four additional models were evaluated using the same complete-case subset (n=396). Areas under the receiver operating characteristic curves (AUCs) were compared using paired DeLong tests in jamovi version 2.6.2.0.

Results: Low FE-1 levels were more frequent among patients with pathological radiological findings than among those with normal findings (31.7% vs. 12.1%; χ^2=45.2, p<0.001; OR=3.38, 95% CI: 2.33–4.89). Among the same 396 complete cases, Model A (age, sex, and radiology) yielded an AUC of 0.694 (95% CI: 0.619–0.769). Adding pancreatic amylase (Model B) increased the AUC to 0.727 (95% CI: 0.657–0.798), although this increase was not statistically significant (ΔAUC=0.0333; DeLong p=0.100). Model C (age, sex, radiology, ALT, glucose, BUN, IgA, and lipase) yielded an AUC of 0.740 (95% CI: 0.672–0.807). Adding pancreatic amylase (Model D) increased the AUC to 0.766 (95% CI: 0.705–0.827), but the increase was not statistically significant (ΔAUC=0.0264; DeLong p=0.107).

Conclusion: Low FE-1 levels were associated with radiological, metabolic, nutritional, and laboratory abnormalities. Pancreatic amylase was independently associated with low FE-1 levels in the expanded regression model; however, its incremental contribution to AUC was not statistically significant when the models were compared using data from the same patients. These findings reflect factors associated with low FE-1 levels and should not be interpreted as establishing a diagnostic model for exocrine pancreatic insufficiency (EPI).

Keywords: Biomarkers, exocrine pancreatic insufficiency, feces, logistic models, pancreatic elastase

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Exocrine pancreatic insufficiency (EPI) develops when the pancreas fails to secrete adequate amounts of digestive enzymes, resulting in symptoms such as maldigestion, malabsorption, chronic diarrhea, steatorrhea, weight loss, and nutritional deficiencies [1]. The reference standards for diagnosis—the secretin stimulation test and 72-hour quantitative

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fecal fat analysis—are accurate but invasive, costly, and largely impractical outside specialized centers [2]. Consequently, fecal elastase-1 (FE-1) has emerged as the primary noninvasive screening tool for EPI in routine clinical practice [3, 4].

As a pancreatic acinar enzyme that remains largely stable during intestinal transit, FE-1 serves as a reliable indirect indicator of exocrine pancreatic function. Recent pooled meta-analytic estimates indicate a sensitivity of approximately 90–94% and a specificity of approximately 69–82% for detecting EPI using the conventional threshold of 200 µg/g, with somewhat higher sensitivity in cystic fibrosis and higher specificity in chronic pancreatitis [3, 4]. Nevertheless, its diagnostic accuracy decreases in mild-to-moderate disease.

The clinical relevance of EPI extends beyond primary pancreatic disease. Population-based screening among patients with diabetes has revealed severe EPI in 10–30% and moderate EPI in 22–56% of patients with type 1 diabetes, with prevalence rates ranging from 5% to 46% among those with type 2 diabetes, highlighting the close functional relationship between the exocrine and endocrine functions of the pancreas [5].

Although the diagnostic performance of FE-1 has been extensively investigated, relatively few studies have simultaneously examined its associations with imaging findings and a broad panel of laboratory parameters—including hematologic, iron, hepatic, renal, thyroid, lipid, and pancreatic enzyme measurements—in a large, unselected patient population. The present study aims to address this gap by comparing radiological and laboratory profiles across FE-1 categories and using multivariable modeling to identify factors independently associated with abnormal FE-1 results.

Materials and Methods

Study design and population

This single-center retrospective study drew on records from patients tested for FE-1 at the Gastroenterology Outpatient Clinic of a tertiary care university hospital across a five-year window (10 March 2020 to 10 March 2025). Of those screened, 1133 satisfied the eligibility requirements; applying the conventional threshold split them into a normal-value group (≥200 µg/g, n=961, 84.8%) and a low-value group (<200 µg/g, n=172, 15.2%). Inclusion required patients to be 18 years or older, to have a recorded FE-1 result with complete clinical documentation, and to have undergone evaluation for possible EPI. Exclusion criteria comprised insufficient clinical information required for eligibility assessment, age below 18, active flares of inflammatory bowel disease (Crohn's disease or ulcerative colitis), a recent episode of acute gastrointestinal infection, or ongoing chemotherapy or radiotherapy for cancer. The patient flow and the samples used in the original regression models are summarized in Figure 1.

Ethical considerations

Ethical approval for this work was granted by the Institutional Non-Interventional Clinical Research Ethics Committee (Decision No: 485, Date: 26.03.2026; Reference No: E-10840098-50.04-2458), and all procedures adhered to the principles set out in the Declaration of Helsinki.

Study variables

The data collected included patient demographics (age, sex) and radiological status (pathological finding present or absent).

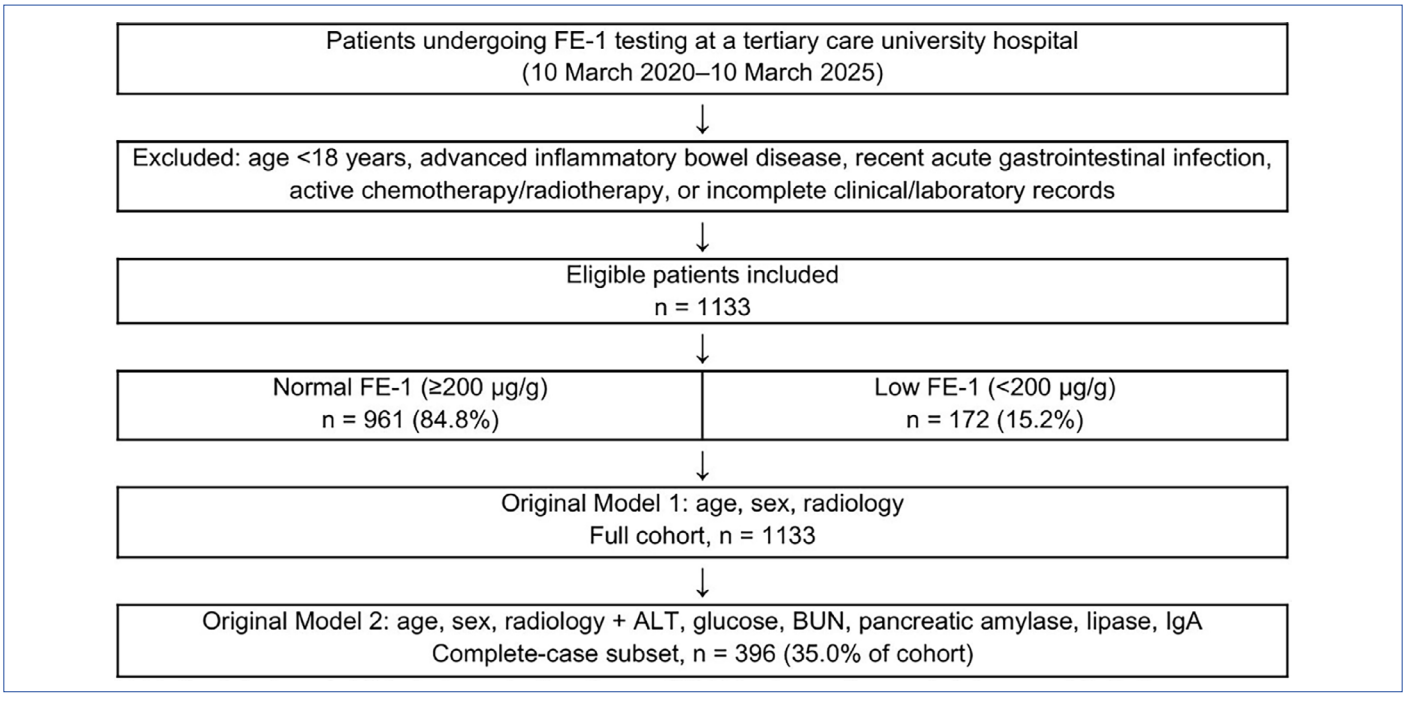

Figure 1. Patient flow diagram showing cohort selection, fecal elastase-1 grouping, and the original regression-model samples.

FE-1: Fecal elastase-1; ALT: Alanine aminotransferase; BUN: Blood urea nitrogen; IgA: Immunoglobulin A.

The laboratory panel was extensive. Hematologic parameters covered leukocyte, erythrocyte, hemoglobin, hematocrit, and erythrocyte-index values along with platelet, neutrophil, lymphocyte, monocyte, and eosinophil counts. Iron-related measures included serum iron, ferritin, unsaturated iron-binding capacity (UIBC), folic acid, vitamin B12, and vitamin D. Immunological testing captured immunoglobulin A (IgA) and anti-tissue transglutaminase IgA. Hepatic parameters spanned alanine aminotransferase (ALT, EC 2.6.1.2), aspartate aminotransferase (AST, EC 2.6.1.1), gamma-glutamyltransferase (GGT, EC 2.3.2.2), alkaline phosphatase, total and direct bilirubin, albumin, and total protein, while renal assessment relied on creatinine and blood urea nitrogen (BUN). Electrolyte values (calcium, sodium, potassium) and inflammatory indices (C-reactive protein, erythrocyte sedimentation rate) were also recorded, as were thyroid parameters (thyroid-stimulating hormone [TSH], free triiodothyronine, free thyroxine) and the lipid panel (low-density lipoprotein, high-density lipoprotein, triglycerides, total cholesterol). Pancreatic enzyme activity was assessed via pancreatic amylase (EC 3.2.1.1) and lipase (EC 3.1.1.3), and tumor markers included CA 19-9, carcinoembryonic antigen, and alpha-fetoprotein. Fecal elastase-1 (EC 3.4.21.36) was quantified using the ElaFast rapid immunochromatographic assay (Eurospital S.p.A., Trieste, Italy).

Laboratory analyses

Stool samples underwent EasyCal extraction before FE-1 quantification with a rapid immunochromatographic assay kit (ElaFast, Eurospital S.p.A., Trieste, Italy), following the manufacturer's protocol; results were classified as severe (<100 µg/g), mild-to-moderate (100–200 µg/g), or normal (>200 µg/g). A Roche cobas c 303/503/703 platform (Roche Diagnostics GmbH, Mannheim, Germany) was used for albumin, ALT and AST (International Federation of Clinical Chemistry [IFCC] methodology), C-reactive protein (Tina-quant C-Reactive Protein IV, immunoturbidimetric technique), iron (Iron Gen.2 assay) and UIBC (Unsaturated Iron-Binding Capacity assay), and IgA (Tina-quant IgA Gen.2 assay). Vitamin B12 levels were determined via electrochemiluminescence immunoassay (Elecsys Vitamin B12 II, cobas e 402/801, Roche Diagnostics GmbH, Mannheim, Germany), and anti-tissue transglutaminase IgA was quantified by enzyme-linked immunosorbent assay on the Alegria® system (ORGENTEC Diagnostika GmbH, Mainz, Germany).

Statistical analysis

Normality of continuous data was evaluated via Shapiro-Wilk testing, after which group comparisons used an independent t-test (normal data) or Mann-Whitney U test (non-normal data); chi-square testing handled categorical comparisons. For univariable laboratory comparisons, all available observations for each parameter were used; the variable-specific sample sizes for the normal and low FE-1 groups are reported in Table 1. The outcome in all logistic regression models was low FE-1 (<200 µg/g). Original Model 1 included age, sex, and radiological status and was fitted in the full cohort (n=1133). Original Model 2 included age, sex, radiological status, ALT, glucose, BUN, pancreatic amylase, lipase, and IgA and was fitted using complete-case analysis (n=396), because only these patients had data available for all variables in that model. Because the original models used different samples, their AUCs were not interpreted as a direct estimate of incremental value. A separate complete-case analysis was therefore conducted in the same 396 patients: Model A included age, sex, and radiological findings; Model B added pancreatic amylase; Model C included Model A plus ALT, glucose, BUN, IgA, and lipase; and Model D added pancreatic amylase to Model C. AUCs with 95% confidence intervals were compared using paired DeLong tests, with B versus A and D versus C assessing the incremental discriminative contribution of pancreatic amylase. Complete cases were compared with the 737 excluded patients for age, sex, radiological status, and FE-1 category using the independent t-test or chi-square test, as appropriate. SPSS Statistics version 24.0 was used for the primary analyses and jamovi version 2.6.2.0 for paired DeLong comparisons. A p-value<0.05 was considered statistically significant; the statistical significance of AUC differences was distinguished from their magnitude and potential clinical relevance. Reporting followed STROBE guidance.

Results

Descriptive findings

Of the 1133 patients in the study cohort, 55.1% (n=624) were female and 44.9% (n=509) were male. FE-1 fell within the normal range for 84.8% (n=961) and was abnormal for 15.2% (n=172). Imaging was unremarkable in 84.1% (n=953) of cases and showed a pathological finding in the remaining 15.9% (n=180) (Fig. 1).

Categorical associations

Sex distribution did not differ meaningfully across the two FE-1 categories (χ^2=1.65, df=1, p=0.198). Radiological abnormality was associated with low FE-1: 31.7% of patients with pathological imaging had low FE-1, compared with 12.1% of those with normal imaging (χ^2=45.2, df=1, p<0.001, OR=3.38, 95% CI 2.33–4.89) (Table 2).

Numerical comparisons

Table 1 presents all available numerical parameters with variable-specific sample sizes for each FE-1 group. The low-FE-1 group displayed lower iron alongside higher UIBC—a pattern consistent with iron deficiency—together with elevated eosinophil count, IgA, ALT, AST, GGT, glucose, and BUN, and reduced platelet count and TSH. No meaningful difference emerged for hemoglobin, leukocyte, neutrophil, or lymphocyte counts, albumin, C-reactive protein, the lipid panel, or the other renal indices (creatinine, calcium, sodium, and potassium).

Logistic regression analyses

The original Model 1, built on age, sex, and radiological status across the full cohort (n=1133), was statistically significant (omnibus χ^2=42.91, df=3, p<0.001; Nagelkerke R^2=0.065) and showed acceptable calibration (Hosmer-Lemeshow statistic=4.05, df=8, p=0.853), although discrimination was modest (AUC=0.635, 95% CI 0.587–0.682); pathological radiology

Table 1. Comparison of numerical parameters between normal and low fecal elastase-1 (FE-1) groups

Parameter	Normal FE-1 n	Normal FE-1 Median (IQR)	Low FE-1 n	Low FE-1 Median (IQR)	p
Age (years), median*	632	37	121	39	0.029
WBC ($\times10^3$/μL)	632	7.05 (2.67)	121	6.89 (2.52)	0.559
RBC ($\times10^6$/μL)	632	4.79 (0.772)	121	4.9 (0.79)	0.478
Hemoglobin (g/dL)	632	13.8 (2.4)	121	14.3 (2.5)	0.224
Hematocrit (%)	632	40.7 (6.03)	121	41.7 (5.9)	0.173
MCV (fL)	632	85.1 (5.5)	121	85.1 (6.4)	0.691
MCH (pg)	632	29.2 (2.3)	121	29 (2.5)	0.954
MCHC (g/dL)	632	34.1 (1.6)	121	34 (1.9)	0.586
Platelet count ($\times10^3$/μL)	632	261 (79)	121	249 (77)	0.049
RDW-CV (%)	632	12.8 (1.1)	121	12.8 (1.1)	0.995
Neutrophil count ($\times10^3$/μL)	632	3.93 (1.99)	121	3.86 (2.08)	0.196
Lymphocyte count ($\times10^3$/μL)	632	2.26 (0.842)	121	2.29 (0.87)	0.443
Monocyte count ($\times10^3$/μL)	632	0.55 (0.25)	121	0.54 (0.22)	0.944
Eosinophil count ($\times10^3$/μL)	632	0.14 (0.14)	121	0.17 (0.18)	0.009
Iron (μg/dL)	156	84 (52.5)	26	62.5 (62.8)	0.013
Ferritin (ng/mL)	159	37.6 (84.9)	28	20.8 (62.7)	0.092
UIBC (μg/dL)	159	256 (112)	26	306 (99.3)	0.006
Folic acid (ng/mL)	151	6.4 (4.1)	25	6.6 (3.8)	0.949
Vitamin B12 (pg/mL)	153	404 (256)	25	408 (181)	0.841
Vitamin D (ng/mL)	71	25.4 (17.4)	8	21.8 (9.43)	0.398
IgA (mg/dL)	530	170 (87.8)	102	187 (105)	0.049
Anti-tTG IgA (RU/mL)	494	1 (0)	96	1 (0)	0.244
ALT (U/L)	574	20 (17)	115	25 (23)	0.004
AST (U/L)	575	20 (7)	115	22 (8)	0.021
GGT (U/L)	579	15 (16)	116	19 (19.5)	0.034
ALP (U/L)	580	65 (26)	117	65 (30)	0.217
Total bilirubin (mg/dL)	430	0.45 (0.307)	106	0.46 (0.313)	0.537
Direct bilirubin (mg/dL)	581	0.23 (0.13)	115	0.25 (0.15)	0.269
Albumin (g/dL)	556	4.76 (0.38)	111	4.77 (0.33)	0.951
Total protein (g/dL)	538	7.45 (0.54)	107	7.52 (0.515)	0.131
Glucose (mg/dL)	439	93 (11)	90	96.5 (11.8)	<0.001
Creatinine (mg/dL)	569	0.76 (0.23)	113	0.81 (0.25)	0.255
BUN (mg/dL)	563	11 (4)	113	12 (4)	0.011
Calcium (mg/dL)	560	9.71 (0.513)	112	9.79 (0.49)	0.463
Sodium (mEq/L)	553	139 (3)	109	139 (2)	0.296
Potassium (mEq/L)	562	4.42 (0.417)	110	4.42 (0.38)	0.592
C-reactive protein (mg/L)	602	1.29 (2.93)	118	1.44 (2.13)	0.449
Erythrocyte sedimentation rate (mm/h)	18	6.5 (17.3)	3	3 (14)	0.390
TSH (μIU/mL)	533	1.71 (1.27)	107	1.47 (1.03)	0.024
Free T3 (pg/mL)	434	3.12 (0.57)	100	3.14 (0.543)	0.394
Free T4 (ng/dL)	434	1.21 (0.228)	101	1.19 (0.2)	0.990
LDL (mg/dL)	371	126 (45)	79	125 (46.5)	0.913
HDL (mg/dL)	334	49 (21)	72	47.5 (21)	0.434
Triglycerides (mg/dL)	381	93 (82)	79	102 (74.5)	0.688
Total cholesterol (mg/dL)	350	194 (50)	74	188 (48.5)	0.801
Pancreatic amylase (U/L)	515	28 (15.1)	108	29 (16)	0.186
Lipase (U/L)	513	33 (15.5)	110	33.3 (20.4)	0.977
CA 19-9 (U/mL)	16	15.4 (15.4)	1	10.7 (0)	—
CEA (ng/mL)	15	1.87 (2.76)	1	1.22 (0)	—
AFP (ng/mL)	8	1.98 (1.56)	1	2.8 (0)	—

P values are based on the Mann-Whitney U test. *: Median only (25^{th}–75^{th} percentile not available for age). Sample sizes (n) are reported separately for each parameter because laboratory data availability varied across the retrospective cohort. For CA 19-9, CEA, and AFP, between-group p values were not calculated because only one observation was available in the low FE-1 group. IQR: Interquartile range; AFP: Alpha-fetoprotein; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CA 19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; FE-1: Fecal elastase-1; GGT: Gamma-glutamyltransferase; HDL: High-density lipoprotein; IgA: Immunoglobulin A; LDL: Low-density lipoprotein; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; MCV: Mean corpuscular volume; RBC: Red blood cell; RDW-CV: Red cell distribution width-coefficient of variation; T3: Triiodothyronine; T4: Thyroxine; tTG: Tissue transglutaminase; TSH: Thyroid-stimulating hormone; UIBC: Unsaturated iron-binding capacity; WBC: White blood cell.

Table 2. Categorical comparisons between normal and low fecal elastase-1 groups

Variable	Normal FE-1 n (%)	Low FE-1 n (%)	χ^2 (df)	OR (95% CI)	p
Female (n=624)	537 (86.1)	87 (13.9)	1.65 (1)	1.24 (0.89–1.71)	0.198
Male (n=509)	424 (83.3)	85 (16.7)	ref.	ref.	—
Radiology normal (n=953)	838 (87.9)	115 (12.1)	45.2 (1)	3.38 (2.33–4.89)	<0.001
Radiology pathological (n=180)	123 (68.3)	57 (31.7)	ref.	ref.	—

Percentages are row percentages (proportion within each sex/radiology subgroup that fell into the normal or low FE-1 group). FE-1: Fecal elastase-1; df: Degrees of freedom; OR: Odds ratio; CI: Confidence interval; ref.: Reference category.

Table 3. Multivariable logistic regression models for factors associated with low fecal elastase-1

Variable	Model 1			Model 2		
	OR	95% CI	p	OR	95% CI	p
Radiology (pathological)	3.221	2.216–4.684	<0.001	5.056	2.773–9.222	<0.001
Age	1.013	0.998–1.028	0.079	1.001	0.972–1.031	0.938
Sex	1.238	0.888–1.726	0.207	1.351	0.745–2.449	0.322
Glucose				1.015	0.989–1.041	0.265
BUN				1.007	0.920–1.103	0.874
Pancreatic amylase				1.031	1.004–1.059	0.026
IgA				1.003	1.000–1.007	0.065
ALT				1.008	0.997–1.019	0.155
Lipase				0.984	0.965–1.005	0.129

Model 1: age, sex, radiology (n=1133). Model 2: age, sex, radiology, ALT, glucose, BUN, pancreatic amylase, lipase, IgA (n=396). Reference categories: radiology = normal (0); sex = female. ALT: Alanine aminotransferase; BUN: Blood urea nitrogen; CI: Confidence interval; IgA: Immunoglobulin A; OR: Odds ratio.

Table 4. Discrimination of same-sample models and pairwise DeLong comparisons in complete cases (n=396)

Analysis	Model/comparison	AUC / ΔAUC	SE	95% CI	z	p
Model performance	Model A	0.694	0.0384	0.619–0.769	—	<0.001
Model performance	Model B	0.727	0.0358	0.657–0.798	—	<0.001
Model performance	Model C	0.740	0.0346	0.672–0.807	—	<0.001
Model performance	Model D	0.766	0.0310	0.705–0.827	—	<0.001
DeLong comparison	Model A vs. Model B	-0.0333	—	-0.0729–0.00638	-1.644	0.100
DeLong comparison	Model A vs. Model C	-0.0454	—	-0.0919–0.00117	-1.911	0.056
DeLong comparison	Model D vs. Model A	0.0717	—	0.02203–0.1214	2.829	0.005
DeLong comparison	Model B vs. Model C	-0.0121	—	-0.0712–0.04708	-0.400	0.689
DeLong comparison	Model B vs. Model D	-0.0384	—	-0.0817–0.00478	-1.743	0.081
DeLong comparison	Model C vs. Model D	-0.0264	—	-0.0584–0.00572	-1.611	0.107

Model A: age, sex, and radiology; Model B: Model A + pancreatic amylase; Model C: Model A + ALT, glucose, BUN, IgA, and lipase; Model D: Model C + pancreatic amylase. AUC: Area under the receiver operating characteristic curve; CI: Confidence interval; SE: Standard error; ΔAUC: Difference in area under the curve.

was the only independent correlate (Table 3). Original Model 2, fitted to the complete-case subset (n=396) and including age, sex, radiological status, ALT, glucose, BUN, pancreatic amylase, lipase, and IgA, was also significant (omnibus χ^2=49.48, df=9, p<0.001; Nagelkerke R^2=0.196), showed good calibration (Hosmer-Lemeshow statistic=4.61, df=8, p=0.798), and had an AUC of 0.761 (95% CI 0.700–0.822). Pancreatic amylase was independently associated with low FE-1 (OR=1.031, 95% CI 1.004–1.059, p=0.026). Because these original models used different samples, their AUC difference was not used to infer incremental contribution (Fig. 1).

In the same 396 complete cases, Model A (age, sex, radiology) yielded an AUC of 0.694 (95% CI 0.619–0.769). Model B, which additionally included pancreatic amylase, yielded an AUC of 0.727 (95% CI 0.657–0.798); the AUC increase of 0.0333 was not statistically significant (DeLong p=0.100). Model C (age, sex, radiology, ALT, glucose, BUN, IgA, and lipase) yielded an AUC of 0.740 (95% CI 0.672–0.807). Model D, which added pancreatic amylase to Model C, yielded an AUC of 0.766 (95% CI 0.705–0.827); the AUC increase of 0.0264 was also not statistically significant (DeLong p=0.107). Model D discriminated better than Model A (ΔAUC=0.0717, 95% CI 0.0220–0.1214; DeLong p=0.005), indicating that the combined expanded model improved discrimination, whereas an incremental AUC contribution attributable specifically to pancreatic amylase was not statistically demonstrated (Table 4).

Table 5. Comparison of complete cases included in the expanded modeling and patients excluded because of missing model data

Variable	Complete cases (n=396)	Excluded (n=737)	p
Age, mean (SD), years	38.5 (10.0)	39.4 (11.1)	0.176
Female sex, n (%)	219 (55.3)	405 (55.0)	0.910
Normal radiological findings, n (%)	319 (80.6)	634 (86.0)	0.016
Normal FE-1, n (%)	328 (82.8)	633 (85.9)	0.171

Equivalent pathological-radiology proportions were 19.4% and 14.0%, and low-FE-1 proportions were 17.2% and 14.1%, respectively. FE-1: Fecal elastase-1; SD: Standard deviation.

Of the 1133 patients, 396 had complete data for all variables required for expanded modeling and 737 did not. Complete cases and excluded patients did not differ significantly in age (38.5±10.0 vs. 39.4±11.1 years; p=0.176), female sex (55.3% vs. 55.0%; p=0.910), or low FE-1 prevalence (17.2% vs. 14.1%; p=0.171). Pathological radiological findings were more frequent among complete cases than excluded patients (19.4% vs. 14.0%; p=0.016), indicating a potential difference in the representativeness of the complete-case subset. These comparisons are summarized in Table 5.

Discussion

Across the 1133 patients studied here, a low FE-1 value went hand in hand with abnormal imaging, an iron-deficiency profile, mildly raised liver enzymes, elevated glucose, and reduced platelet and TSH levels. Viewed together, these associations point to something broader than an isolated pancreatic abnormality — low FE-1 in this cohort appears to be associated with a wider metabolic and nutritional disturbance.

Of all variables tested, radiological abnormality carried the strongest independent association with low FE-1 (OR=3.22) — a result consistent with prior evidence tying fecal elastase to structural pancreatic pathology. In a series of 40 patients with low FE-1 who went on to endoscopic ultrasound, 82.5% received a new pancreatic diagnosis, chronic pancreatitis being the most frequent [6], reinforcing the connection between abnormal elastase and demonstrable structural disease. That said, Model 1's modest AUC (0.635) indicates age, sex, and imaging together predict low FE-1 only weakly, in keeping with the observation that milder exocrine dysfunction does not always produce visible structural change.

Lower iron and higher UIBC in the low FE-1 group showed a pattern suggestive of iron deficiency and may represent an early nutritional warning sign; the 2021 UK consensus guidelines on pancreatic exocrine insufficiency specifically recommend micronutrient screening, including iron status, as part of routine assessment [7]. A recent study in heart-failure patients similarly found EPI to be independently associated with broader micronutrient depletion, reinforcing that impaired exocrine function can signal a systemic nutritional problem rather than a purely pancreatic one [8]. Elevated glucose in the abnormal group mirrors the well-documented interplay between exocrine and endocrine pancreatic function: multicenter screening data reveal a substantially higher rate of EPI among people with diabetes [5], and a UK single-center series similarly counted diabetes mellitus among the extra-pancreatic conditions linked to EPI [9]. Among diabetic patients specifically, fecal elastase has been shown to track positively with serum lipase and C-peptide, tying exocrine status to residual endocrine function at the biomarker level [10]. Further support comes from a cross-sectional study conducted in people with metabolic-associated fatty liver disease, which reported higher glycated hemoglobin among those with EPI along with a further drop in FE-1 among patients who also had diabetes [11]. Because our study is retrospective and cross-sectional, the direction of causality between glucose elevation and reduced elastase cannot be established.

The modest yet significant rise in ALT, AST, and GGT among patients with low FE-1 deserves attention and could reflect how tightly liver and pancreatic physiology are intertwined, both structurally and functionally. A 2020 investigation correlating fecal elastase with liver biopsy findings and pancreatic fat fraction in non-alcoholic fatty liver disease likewise identified exocrine insufficiency as common regardless of diabetes status, proposing a two-way metabolic connection linking the organs [12]. A more recent cross-sectional analysis in metabolic-associated fatty liver disease echoed this, documenting lower FE-1 together with higher ALT, GGT, and alkaline phosphatase, EPI in 84.3% of the sample, and strong discrimination (AUC=0.873) [9]. Mechanistic exploration fell outside our study's scope, but the co-occurrence of raised liver enzymes and depressed FE-1 that we observed fits comfortably within this body of evidence. Pancreatic amylase was independently associated with low FE-1 in the expanded multivariable model. However, in same-sample comparisons, adding pancreatic amylase produced only modest increases in discrimination, which did not reach statistical significance. Thus, its independent association should not be interpreted as demonstrating a significant incremental contribution to model discrimination. This finding parallels a recent multicenter investigation of chronic and autoimmune pancreatitis patients, which concluded that while normal p-amylase and lipase levels do not exclude exocrine insufficiency, reduced values in either enzyme warrant further work-up for coexisting EPI [13].

Practically speaking, these results argue for a multi-parameter strategy when deciding which patients merit further pancreatic work-up. Current expert guidance stresses that no single non-invasive marker reliably captures mild-to-moderate EPI on its own, and instead recommends raising clinical suspicion whenever several signals converge — unexplained iron deficiency, unexplained transaminase elevation, new or worsening hyperglyce-

mia, and imaging abnormalities — rather than relying on FE-1 alone [14]. Although the expanded model showed greater discrimination than the basic model, these original models were fitted in different patient samples and therefore their AUC difference should not be interpreted as an incremental effect. These routinely available variables may help identify patients in whom further pancreatic evaluation could be considered; however, their clinical utility requires prospective validation.

A number of limitations warrant mention. Because the design was retrospective and confined to one center, causal conclusions cannot be drawn. Model 2 relied on a complete-case subset (n=396) representing only around a third of the full cohort, which could restrict generalizability and introduce selection bias. Imaging modality and the specific criteria used for radiological assessment were not specified in the dataset, so that particular result merits cautious interpretation. Lastly, FE-1 was measured only once per patient and was not verified against a reference pancreatic function test; confirming these findings will require prospective work across multiple centers.

Conclusion

Taken together, this large-cohort analysis links abnormal FE-1 to pathological imaging, a pattern suggestive of iron deficiency, mild liver enzyme elevation, higher glucose, and — once multivariable adjustment was applied — higher pancreatic amylase. Pancreatic amylase was independently associated with low FE-1 in the expanded multivariable model. However, its addition resulted in only modest, statistically non-significant improvements in discrimination in same-sample comparisons. These findings support an association between pancreatic amylase and low FE-1 but do not establish a significant incremental predictive contribution. Prospective validation is needed to determine whether these findings may aid the clinical evaluation of patients with suspected pancreatic exocrine dysfunction.

Disclosures

Ethics Committee Approval: The study was approved by the Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee (no: 485, date: 26/03/2026).

Informed Consent: The requirement for informed consent was waived by the ethics committee because this retrospective study used existing medical records.

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