Elevated Amylase and Lipase Levels in the Neurosurgery Intensive Care Unit

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Background: Multiple factors may affect pancreatic enzyme levels even in the absence of pancreatitis. In the general intensive care unit (ICU), we examined the incidence, various clinical factors, and sequelae associated with elevated pancreatic enzymes in the neurosurgery ICU.

Methods: Eighty-nine patients who were admitted to the neurosurgery ICU with gastrointestinal symptoms and signs from January to October 2007 were classified into 2 groups according to their pancreatic enzymes as follows: normal pancreatic enzyme levels ($n = 46$) and elevated levels ($n = 43$). We analyzed the general data, including sex, age, indications for admission, types of surgery, initial Glasgow coma scale (GCS) score, neurosurgery ICU-stay days, and mechanical ventilator-use days. We also collected data on vital signs, serum markers, and drug prescriptions. Radiological examinations, including sonography and computed tomography (CT) scans of the abdomen were performed.

Results: Nearly half of the patients who were admitted to the neurosurgical ICU with gastrointestinal symptoms and signs had elevated serum pancreatic enzymes. Elevated pancreatic enzyme levels were significantly associated with anemia ($p = 0.048$) and renal failure ($p = 0.026$), and were not associated with sex, age, indications for admission, types of surgery, initial GCS, neurosurgery ICU-stay days, mechanical ventilator-use days, hypotension, fever, usual ICU drugs, and other serum hepatic markers. High pancreatic enzyme levels were associated with a high mortality ($p = 0.02$). Abdominal CT had a high positive-predictive rate for the diagnosis of pancreatitis (63%).

Conclusion: Various neurosurgery events and diagnoses may lead to different degrees of serum pancreatic enzyme elevation. Patients with elevated pancreatic enzyme levels have a higher mortality rate than those with normal enzyme levels. We believe that abdominal CT should be indicated for patients if their amylase levels are more than 3-fold the upper normal limit and lipase levels are more than 5-fold. [*J Chin Med Assoc* 2010;73(1):8–14]

Key Words: amylase, elevated pancreatic enzyme, intensive care unit, lipase, neurosurgery, pancreatitis

Introduction

Little is known about pancreatic enzyme levels in the neurosurgery intensive care unit (ICU). Although a number of related issues have emerged in the general ICU, some of which remain unclear,[1,2] clinically, we still use the concepts derived from the general ICU to manage neurosurgical patients who have elevated pancreatic enzymes. Bouwman et al noted that hyperamylasemia may be a result of intracranial bleeding.[3] Severe head injury can activate pathways that increase amylase levels in the blood, suggesting central nervous system regulation of serum amylase levels.[4] The purpose of this study was to look at the effects of elevated pancreatic enzymes in the neurosurgical ICU. Two issues that need to be resolved are: (1) whether we can assess the specific characteristics of this group of patients with elevated pancreatic enzymes; and (2) whether we can incorporate such information into the way we manage this group of patients.

Methods

This was a retrospective study performed in the neurosurgery ICU. There were 573 patients admitted to the neurosurgery ICU from January to October 2007. The subjects were 89 patients (15.53%) who had

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gastrointestinal symptoms and signs. Gastrointestinal symptoms included abdominal pain, abdominal fullness, poor appetite, poor gastric emptying, poor absorption, or unexplained back pain. Gastrointestinal signs included ileus, ascites, abnormal stools (color, density, texture), unknown fever, or vital sign changes when patients were moved or their abdomens were touched. Because of the altered consciousness of these patients, these symptoms and signs were observed by neurosurgery ICU staff. We collected general data including sex, age, indications for admission to the neurosurgery ICU, types of surgery, initial Glasgow coma scale (GCS) score, days in the neurosurgery ICU, and mechanical ventilator (MV)-use days. We also collected data on vital signs (body temperature and blood pressure), various serum markers [amylase, lipase, hemoglobin, creatinine, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and glucose levels], and drug prescriptions (propofol, perdipine, steroids, and nimodipine). In indicated patients, we performed abdominal sonography and computed tomography (CT) to confirm the diagnosis of pancreatitis or other pathological lesions in the abdomen. The indications for radiological examination included highly suspected pancreatitis (symptoms, signs, elevated amylase levels > 3-fold the upper normal limit, or elevated lipase levels > 5-fold the upper normal limit), positive peritoneal signs, and fever of unknown origin.

The 89 patients were categorized into Group I and Group II by their amylase and lipase levels. Group I included patients who had normal levels of pancreatic enzymes (both amylase and lipase). Group II indicated those patients who had elevated pancreatic enzyme levels (amylase > 190 U/L or lipase > 200 U/L). We defined clinical events as the following: anemia (hemoglobin < 10 mg/dL), renal failure (serum creatinine > 1.5 mg/dL), hypotension (systolic blood pressure < 100 mmHg), and fever (body temperature > 38°C).

SPSS statistical software (SPSS Inc., Chicago, IL, USA) was used for analysis. Fisher's exact test was used to compare sex, mortality, hypotension, fever, anemia, renal failure, and drug prescription of propofol, perdipine, steroid, and nimodipine. For continuous measurements such as age, ICU-stay days, MV-use days, initial GCS score, minimal serum albumin levels, maximal serum ALT/AST levels, and maximal serum glucose levels, independent *t* tests or nonparametric analyses were used. Pearson's χ^2 test was used to compare abdominal sonography and CT findings.

Results

The patients were categorized into 2 groups; there were 46 patients (51.7%) in Group I and 43 patients (48.3%) in Group II. The results were analyzed in 5 parts: general data, clinical events, lab data, prescribed drug effects, and radiological results.

Causes of admission

The indications for admission were divided into 8 major etiologies: subarachnoid hemorrhage, emergent surgery, elective surgery, respiratory failure, spontaneous intracerebral hemorrhage, severe head injury, spinal disease or spinal trauma, and others. Respiratory failure due to neurological causes, such as cervical spinal injury and severe head trauma-induced respiratory failure, was not included in this study. Table 1 shows the average amylase and lipase levels of neurosurgery ICU patients. Kruskal-Wallis tests revealed no significant differences among the 8 groups. We found that the average levels of pancreatic enzymes were higher in brain insult patients compared to patients with other causes of admission ($p = 0.04$).

Table 1. Mean maximal amylase/lipase levels in neurosurgery ICU patients

Diagnosis	*n*	Amylase level, mg/dL ($p = 0.579$*)	Lipase level, mg/dL ($p = 0.326$*)
SAH and other vascular disease	23	337.43 ± 256.49	551.86 ± 853.01
Emergent surgery	23	304.35 ± 269.98	289.55 ± 289.03
Elective surgery	17	207.65 ± 142.90	136.38 ± 135.90
Respiratory failure†	9	196.22 ± 116.94	168.33 ± 132.05
Spontaneous ICH	6	361.83 ± 252.92	853.60 ± 1,143.38
Severe head injury	5	460.40 ± 543.81	1,027.25 ± 1,642.99
Spinal disease or spinal trauma	4	151.75 ± 65.03	187.33 ± 112.61
Others‡	2	340.50 ± 381.13	748.50 ± 972.27

**Kruskal Wallis test; †the causes of respiratory failure excluded neurological causes such as cervical spinal injury and severe head trauma; ‡others = 2 patients who had tumor bleeding during operation and admission. ICU = intensive care unit; SAH = subarachnoid hemorrhage; ICH = intracerebral hemorrhage.*

Surgical intervention

There were 71 patients who received surgical intervention in this study. Patients who received specific surgical intervention were divided into 7 major procedures: craniotomy for trauma or intracerebral hemorrhage aneurysm clipping or other vascular surgeries, craniotomy for tumors, external ventricular drainage (EVD)/intracranial pressure monitor/ventriculoperitoneal shunt, spinal surgery, the transsphenoidal approach, and craniectomy. The average levels of pancreatic enzymes were higher in aneurismal-related procedures, such as clipping or external ventricular drain insertion, but there was no significant difference compared to other neurosurgical interventions (Table 2).

Demographic data

There was a significant correlation between peak amylase and lipase levels ($p < 0.001$; Table 3). There were no differences in the age or sex of the patients, initial GCS score, ICU admission days, or MV-use days between Groups I and II. Mortality was significantly higher in Group II patients than in Group I patients.

Clinical events

Group II patients had a greater incidence of anemia and renal failure before pancreatic enzymes approached their peak level ($p < 0.05$; Table 4). There were no significant differences in incidence rates of hypotension and fever between the 2 groups.

Serum hepatic and bile duct markers

We investigated other related serum markers because sometimes pancreatitis is induced by hepatic or gallbladder disorders.[2] However, there were no significant differences in serum albumin, AST, ALT, and glucose levels between Group I and Group II (Table 5).

Prescribed drug effects

There was no significant elevation in pancreatic enzymes after propofol ($p = 0.654$), perdipine ($p = 0.107$), dexamethasone ($p = 0.505$), or nimodipine ($p = 0.582$) use.

Table 2. Mean maximal amylase/lipase levels for different neurosurgical interventions

Surgery	*n*	Amylase level, mg/dL ($p = 0.380$*)	Lipase level, mg/dL ($p = 0.526$*)
Craniotomy for trauma or ICH	20	243.75 ± 193.39	368.32 ± 644.60
Aneurysm clip or other vascular surgery	17	366.71 ± 283.18	550.53 ± 824.72
Craniotomy for tumor	14	231.29 ± 147.36	148.92 ± 148.54
EVD/ICP monitor/VP shunt	13	348.08 ± 287.91	547.08 ± 680.28
Spinal surgery	5	228.60 ± 180.83	170.00 ± 98.27
TSA†	1	104	71
Craniectomy†	1	754	313
None	18	272.72 ± 320.565	427.71 ± 851.34

**Kruskal Wallis test; †TSA and craniectomy were not listed for comparison because of the low number of samples. ICH = intracerebral hemorrhage; EVD/ICP = external ventricular drainage/intracranial pressure; VP = ventriculoperitoneal; TSA = transsphenoidal approach.*

Table 3. Demographic data*

	Group I ($n = 46$)	Group II ($n = 43$)	*p*
Age (yr)	62.59 ± 14.633	61.95 ± 16.560	0.849†
Sex (male)	29 (63.0)	31 (72.1)	0.377‡
Mortality	8 (17.4)	17 (39.5)	0.033‡
ICU stay (d)	22.68 ± 19.37	25.56 ± 15.68	0.538†
MV use (d)	21.29 ± 20.56	18.86 ± 13.60	0.700†
Initial GCS score	10.72 ± 4.410	10.62 ± 3.825	0.912†
Peak amylase level (mg/dL)	118.04 ± 45.767	474.14 ± 255.592	< 0.0001†
Peak lipase level (mg/dL)	109.79 ± 83.168	687.03 ± 857.015	< 0.0001†

**Data presented as mean ± standard deviation or n (%); †independent samples t test; ‡Fisher's exact test. ICU = intensive care unit; MV = mechanical ventilator; GCS = Glasgow coma scale.*

Radiological results

Thirty-four patients received abdominal sonography or CT (Table 6). The relationships between radiological findings and pancreatic enzyme levels and mortality are shown in Table 7.

In a previous study of pancreatitis,[2] the average amylase level in a confirmed diagnosis was approximately 3 times the upper normal limit, and the average lipase level was approximately 5 times. Therefore, we set 3 times and 5 times as the upper normal limits of amylase and lipase, respectively, as cut-off points to divide the patients into 3 groups (normal, mildly elevated, and elevated pancreatic enzyme levels). When correlating the radiological findings with the pancreatic enzyme levels, we found that the higher the pancreatic enzyme level, the more severe the radiological finding (Tables 8 and 9).

Table 10 shows the positive (sensitivity) and negative (specificity) predictive rates for abdominal sonography and CT in Groups I and II.

Discussion

Elevated pancreatic enzymes are frequently observed in patients admitted to the neurosurgery ICU without an identifiable pancreatic lesion.[1,3–6] Liu et al noted that 15% of patients had elevated serum amylase and lipase levels at some point during their neurosurgery ICU stay.[6] Justice et al showed that 66% of patients diagnosed with intracranial bleeding had elevated lipase enzyme activity, and 45% had elevated amylase enzyme activity.[5] Vitale et al demonstrated that there was a 38% prevalence of hyperamylasemia in patients with head injury.[4] In our study, we found that different neurological indications for admission have different percentages of elevated pancreatic enzyme levels. Fourteen (61%) patients with subarachnoid hemorrhage and other vascular diseases had elevated pancreatic enzyme levels, as well as 11 (48%) patients who received emergency surgery (Figure 1). We found that patients with brain insults may have higher pancreatic enzyme levels compared with those with non-brain insults. Patients with neurosurgical intervention may have had elevated pancreatic enzymes, but there was no significant difference in the different types of neurosurgical intervention.

Previous studies have revealed some probable factors that are associated with elevated pancreatic enzymes, such as Acute Physiology and Chronic Health Evaluation (APACHE) II score, Multiple Organ Dysfunction Score (MODS), hypotension, fever, anemia, renal failure, total parenteral nutrition use, MV-use days, ICU-stay days, serum transaminase levels, total bilirubin levels, and hemoglobin levels.[2] However, there were differences in neurosurgical patients, in whom the probable factors were age, hospital-stay days,[6] GCS score,[5] not related to shock,[3] total parenteral nutrition use, drugs (steroid, mannitol, ceftriaxone, and nimotop),[5] and mortality.[6] Our study findings were different to those from previous studies, as discussed below.

Table 4. Clinical events*

	Group I ($n = 46$)	Group II ($n = 43$)	p
Hypotension	25 (54.3)	16 (37.2)	0.740
Fever	16 (34.8)	25 (58.1)	0.286
Anemia	31 (67.4)	37 (86.0)	0.048†
Renal failure	4 (8.7)	12 (27.9)	0.026†

Data presented as n (%); †Fisher's exact test. Hypotension = systolic blood pressure < 100 mmHg; fever = body temperature > 38 °C; anemia = hemoglobin < 10 mg/dL; renal failure = serum creatinine level > 1.5 mg/dL.

Table 6. Radiological results*

	n	Positive	Negative
Sonography	24	4	20
Abdominal CT	14	7	7

Four cases had both sonography and CT examination, and 9 patients were radiologically positive. CT = computed tomography.

Table 5. Serum hepatic and bile duct markers*

	Group I ($n = 46$)	Group II ($n = 43$)	p†
Alb level (mg/dL)	2.87 ± 0.52	2.77 ± 0.63	0.300
ALT level (mg/dL)	110.63 ± 196.86	115.38 ± 125.84	0.403
AST level (mg/dL)	76.91 ± 99.08	79.35 ± 61.24	0.242
Maximum glucose level (mg/dL)	200.11 ± 73.85	217.70 ± 112.98	0.876

Data presented as mean ± standard deviation; †Mann-Whitney U test. Alb = albumin; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Age and ICU-stay days

Only 1 report[6] from a neurosurgery ward demonstrated that the factors of age and hospital-stay days are related to the elevation of pancreatic enzymes, which is not similar to our study. Liu et al[6] reported that the average ages in their control group and elevated pancreatic enzyme group were 45 and 58 years, respectively. Our patients were older than in the previous study[6] (the average age was 62 years, with no significant difference between the control and experiment groups). Age difference had little effect on elevated pancreatic enzymes levels because of the more complex medical conditions in aged patients.

In our study, elevated pancreatic enzyme levels were not associated with ICU-stay days. We believe that the natural course of neurological disease is different from that of non-neurological disease. ICU-stay days are determined by the neurological condition and not the gastrointestinal condition. We found that the relationship between ICU-stay days and elevated pancreatic enzymes was not significant.

GCS, APACHE II, and MODS score

Only 1 report[5] from a neurosurgery ICU has demonstrated that the GCS score is related to elevated pancreatic enzyme levels. Our results showed that there was no relationship between GCS score and elevated pancreatic enzyme levels. We believe that elevated pancreatic enzyme levels are related to severity classifications such as APACHE II and MODS, and are not related to a single organ failure scale such as the GCS.

Shock

We found that shock was related to an elevation of pancreatic enzyme levels in the general ICU, but not in the neurosurgery ICU. Our results support the

Table 7. Radiological findings versus pancreatic enzyme levels and mortality*

	Radiology(+) ($n = 9$)	Radiology(–) ($n = 25$)	p
Maximum amylase level (mg/dL)	667.44 ± 229.42	313.44 ± 312.31	0.001†
Maximum lipase level (mg/dL)	1,550.11 ± 945.92	368.92 ± 742.08	< 0.001†
Mortality‡	4 (44.4)	10 (40.0)	0.094§

*Data presented as mean ± standard deviation or n (%); †Mann-Whitney U test; ‡the causes of mortality for these 14 patients were brain insults or sepsis, with no intra-abdominal events; §Pearson's χ^2 test.

Table 8. Amylase level versus pancreas findings on abdominal CT

CT	Pancreatic enzyme level ($p = 0.007$*)			
	Normal	Mildly elevated	Elevated	Total
No pancreatitis	3	4	0	7
Mild pancreatitis	0	4	2	6
Moderate pancreatitis	0	0	1	1

*Exact test. CT = computed tomography.

Table 9. Amylase level versus pancreas findings on abdominal sonography

Sonography	Pancreatic enzyme level ($p = 0.003$*)			
	Normal	Mildly elevated	Elevated	Total
No pancreatitis	10	8	2	20
Mild pancreatitis	0	1	3	4

*Exact test.

Table 10. Predictive rate of abdominal sonography/CT in indicated patients

Abdominal sonography ($n = 24$)	Pancreatic enzyme level	
	Normal (Group I)	Elevated (Group II)
Normal pancreas	10	10
Abnormal pancreas	0	4
Predictive rate (negative/positive)	10/10 + 0 = 100%	4/14 = 28%
Abdominal CT ($n = 14$)	**Pancreatic enzyme level**	
	Normal (Group I)	Elevated (Group II)
Normal pancreas	3	4
Abnormal pancreas	0	7
Predictive rate (negative/positive)	3/3 + 0 = 100%	7/11 = 63%

CT = computed tomography.

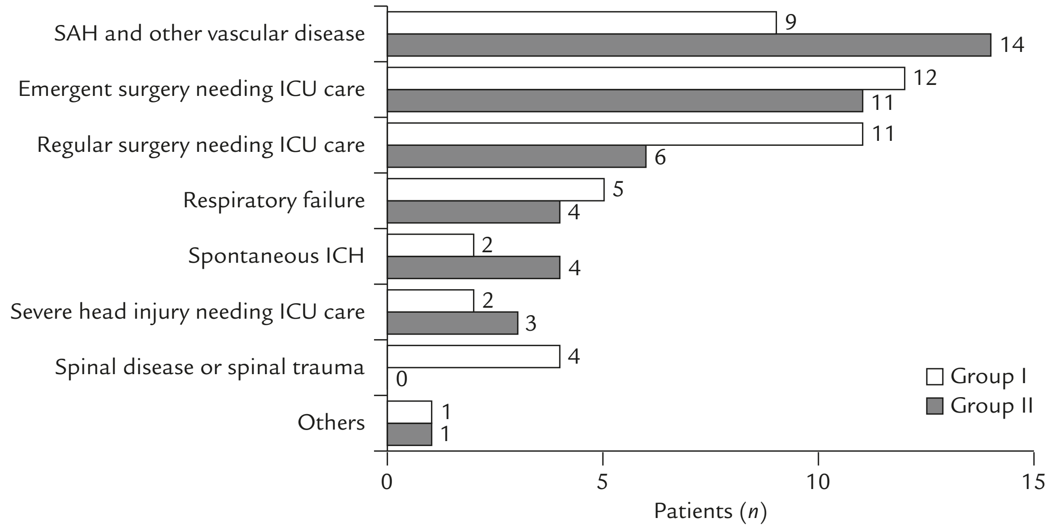

Figure 1. Distribution of different indications for admission in Groups I and II patients. SAH = subarachnoid hemorrhage; ICU = intensive care unit.

findings of a previous study.[4] We believe that the type of shock found in the general ICU and the neurosurgical ICU is different, and neurogenic shock plays a major role. Warshaw and O'Hara found that the pancreas is susceptible to shock and that hyperamylasemia frequently ensues.[7] It is unknown whether hyperamylasemia results from elevated pancreatic isoenzymes or from salivary isoenzymes, and is still a subject of controversy in recent research.[4,7–9] We speculate that septic shock and hypovolemic shock are the usual types of shock in the general ICU, but neurogenic shock plays a larger role in the neurosurgery ICU. We believe that neurogenic shock may have no effect on elevated pancreatic enzyme levels because the duration of shock may not persist long enough under appropriate management. Further studies are needed to quantify autonomic nerve activity to confirm the role of neurogenic shock in elevated pancreatic enzyme levels.

Fever

The causes of fever in the general ICU are usually infection or inflammation. However, dysfunction of the body temperature center plays an important role in patients, rather than the complicated infections and other immune disorders in the general ICU. In general, the more complicated the infection, the higher the pancreatic enzyme levels, which fully explain why fever is related to pancreatic enzymes in the general ICU, but not in the neurosurgery ICU.

Relationship with hepatic and pancreatic diseases

To clarify the possibility of hepatic (or gallbladder disease) hyperamylasemia (i.e. hepatic necrosis may decrease the clearance of amylase) or pancreatitis (i.e. alcoholism or common bile duct stones), we also collected data on serum transaminases, albumin, and glucose levels but found no relationship to pancreatic enzyme levels. Compared with the results from the general ICU,[2] these findings led us to believe that elevated pancreatic enzymes are not related to hepatic-induced hyperamylasemia or pancreatitis. In contrast, there was stronger evidence of elevated pancreatic enzymes resulting from neurogenic causes.

Prescribed drug effects

Drugs had little effect on pancreatic enzyme levels in our study, and these results are compatible with those of a previous study[5] from the neurosurgery ICU. Although many reports have shown that the use of propofol and steroids may result in pancreatitis,[10–15] and that there is elevation of pancreatic enzyme levels, this was not the case in our patients, since elevated pancreatic enzymes were largely not related to pancreatitis.

Parasympathetic motor innervations of both the salivary glands and the pancreas control the cephalic phase of secretion. Stimulation of the brainstem motor nuclei of these nerves by trauma may result in an elevation of blood amylase levels.[16] Sympathetic control of pancreatic secretion is primarily inhibitory via vasoconstriction, which limits the maximal rate of secretion. Loss of sympathetic tone with resultant hyperperfusion may result in increased amylase production after trauma. Moreover, pancreatic polypeptide levels in patients with severe head injury are significantly greater than those in control trauma patients without head injury.[16] These peptides, including gastrin, cholecystokinin, acetylcholine, and norepinephrine, are found in the brain and in the vagus nerve.[8,17–20] Although central nervous system control of amylase and lipase secretion is well described, how lesions of the central nervous system lead to an elevation of amylase and lipase is still poorly understood. Further measurements and observations are needed to define whether the autonomic nervous system is truly excited or inhibited in patients with elevated pancreatic enzymes.

Our radiological results suggested that if a patient has a serum amylase level elevated more than 3-fold the upper normal limit or a lipase level more than 5-fold, abdominal CT should be considered first. Abdominal sonography can also be performed if the patient's condition does not permit CT examination. The typical radiological findings in our neurosurgical patients were mild pancreatitis features, which agree with the mildly elevated pancreatic enzymes. Considering the benefit of enteral nutrition, we suggest continuing feeding if amylase levels are less than 3-fold the upper normal limit and lipase levels are less than 5-fold, and then following up the levels of pancreatic enzymes until pancreatic enzyme levels have declined.

This retrospective study had selection bias. Gastrointestinal symptoms and signs were determined by the doctors and nurses because of patients' altered level of consciousness. Many symptoms were nonspecific, such as "unexplained back pain" and "unknown fever". A more rigorous study design would be a prospective laboratory evaluation of all admissions to the neurosurgery ICU to determine if there are differences between patients with normal serum pancreatic enzyme levels and elevated levels.

In conclusion, elevated pancreatic enzyme levels in the neurosurgery ICU are a complicated condition. Nearly half of the patients admitted to the neurosurgery ICU with gastrointestinal signs had elevated serum pancreatic enzyme levels. Mildly elevated pancreatic enzymes were rarely caused by pancreatitis in the neurosurgery ICU. Various neurosurgical events and diagnoses may lead to a different extent of elevation of serum pancreatic enzymes. This finding was related to anemia and renal failure, but was not related to age, sex, admission stay, MV-use days, GCS score, hypotension and fever. Drug effects were minimal. A higher mortality rate was present in patients with elevated pancreatic enzyme levels. We suggest that abdominal CT should be indicated for patients if their amylase levels are more than 3-fold and lipase levels are more than 5-fold the upper normal limits.

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