

The Early Identification of Patients with Gallstone Associated Pancreatitis Using Clinical and Biochemical Factors Only

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Early differentiation of gallstone from nongallstone associated acute pancreatitis by imaging methods is often difficult. Timing of surgery in gallstone pancreatitis is controversial, but early surgery requires early demonstration of gallstones. This study assesses the value of easily available clinical and laboratory data in establishing gallstones as the etiology of pancreatitis. In 405 consecutive episodes of acute pancreatitis, data were collected prospectively on 14 clinical and laboratory variables. Gallstones caused 177 episodes and alcohol 135, 93 were due to other or unknown causes. Age, sex, and within 48 hours of admission, serum alkaline phosphatase, aminotransferases, amylase, and bilirubin were all significantly different (all $p < 0.001$, chi square) in gallstone and alcohol groups. Multivariate analysis based on five of these variables enabled correct prediction of the presence or absence of gallstones in 50 of a further 56 episodes. This method may help in planning early interventional treatment of gallstone associated acute pancreatitis.

GALLSTONES ARE PRESENT in approximately 50% of patients with acute pancreatitis in the United Kingdom^{1,2} and there is little doubt that they are an important etiological factor. The mortality rate for gallstone-associated acute pancreatitis is 8–12.5%^{1,2} in the course of the same hospital admission, when a policy of initial conservative treatment is used. The concept that cholecystectomy and removal of gallstones reduces substantially the risk of developing further attacks of pancreatitis has not been disputed, but major controversy still surrounds the question of the optimal timing of biliary surgery in patients with gallstone-associated pancreatitis. The options for the timing of surgery include: immediate surgery performed as soon as possible after admission but within 2 to 3 days, early surgery performed during the same admission but after the pancreatitis has clinically settled, and delayed surgery performed at a subsequent admission when there is no evidence of pancreatitis. The relative merits of each option have been reported^{3,4,5,6} and endoscopic papillotomy has been suggested as a satisfactory alternative to surgery in the early treatment of gallstone-associated acute pancreatitis.⁷

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One of the major obstacles to any policy of early biliary tract surgery is the difficulty of accurate detection of gallstones. Standard imaging techniques are often unsatisfactory^{8,9,10} and may be quite misleading^{11,12} in the presence of acute pancreatitis. The present paper evaluates a method of assessment not based on imaging techniques, which might allow diagnosis of the gallstones sufficiently early for implementation of a policy of immediate surgery or endoscopic papillotomy.

Patients and Methods

Data have been collected prospectively on all patients admitted to Glasgow Royal Infirmary with acute pancreatitis since 1971.² Patients in whom a final diagnosis of acute pancreatitis was sustained, and who were admitted between January 1, 1974 and June 30, 1982 form the basis of this report. The diagnosis of acute pancreatitis was accepted if a compatible clinical syndrome was associated with a serum amylase of more than 1200 IU/l. Patients with secondary acute pancreatitis have been described previously and have been excluded.¹³ Five patients in whom a laparotomy diagnosis was made when serum amylase had not been measured have been included.

For the purposes of this review, patients have been divided into two groups. Group A comprises *all* patients who met the criteria of inclusion described and who were admitted between January 1, 1974 and December 31, 1980; these patients provide the data base for the predictive analysis. Group B patients were those admitted between January 1, 1981 and June 30, 1982 who met the criteria for inclusion above and had complete information available on serum amylase, alanine aminotransferase, and alkaline phosphatase within 48 hours of admission.

Age and sex were recorded. Within 48 hours of admission, serum values of amylase, aspartate aminotrans-

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ferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, bilirubin, urea, glucose, lactic dehydrogenase (LDH), calcium, albumin, and white blood cell count (WCC) were determined from samples of venous blood, and arterial oxygen saturation (PaO₂) was measured. For analysis, we have used the highest values of all continuous variable parameters collected during this period with the exception of serum albumin, calcium, and PaO₂, for which the lowest values were used. Amylase levels were measured by the Phadebas method (normal range 70–300 IU/l). Other methods have been described previously.¹⁴

Gallstones were diagnosed by the subsequent demonstration of calculi by standard imaging techniques (oral cholecystography, intravenous cholangiogram, ultrasound, endoscopic retrograde cholangiopancreatography, or percutaneous transhepatic cholangiography), surgery, or autopsy. Failure to demonstrate the gallbladder at oral cholecystography or intravenous cholangiography was not considered diagnostic of gallstones. Alcohol was only accepted as the etiological factor when there was a positive history of heavy alcohol intake within 4 days of admission or a history of prolonged alcohol abuse with further intake of alcohol within 4 days of admission, and when gallstones had been excluded by standard imaging techniques, surgery, or autopsy.

Chi square testing was used to determine the significance of differences in each parameter when the gallstone and alcohol associated pancreatitis groups from Group A were compared. A rounded value close to the midpoint of the median values for the two etiological groups was used as the cutpoint for chi square testing. Data from Group A patients were used as a basis for multivariate analysis using stepwise logistic regression¹⁵ to provide a theoretical probability of gallstones or alcohol as the aetiology of acute pancreatitis. The predictive methods determined from the Group A patients were then applied separately to the Group B patients to validate their accuracy.

Results

Group A Patients

Within the first period of the study, 347 patients (149 men and 198 women) were admitted with a total of 405 episodes of acute pancreatitis. The average age of the patients was 52.3 ± SD 18.6 years; 184 episodes occurred in men and 221 episodes in women. Of the 405 episodes, 177 (44%) were associated with gallstones and 14 of these proved fatal within the same hospital admission (8%). Alcohol was considered the primary etiological factor in 135 episodes (33%) and 12 of these proved fatal within the same hospital admission (9%). Of the remaining 93 episodes, two patients with pancreatic cancer each had

TABLE 1. Significant Factors in Separating Gallstone and Alcohol Associated Acute Pancreatitis

		n	Per Cent with Gallstones	p<
Alkaline phosphatase (IU/l)	<300	141	28	0.001
	≥300	154	86	
Age (years)	<50	147	28	0.001
	≥50	165	82	
ALT (IU/l)	<100	164	34	0.001
	≥100	131	89	
Sex	M	154	31	0.001
	F	158	82	
AST (IU/l)	<100	173	38	0.001
	≥100	123	87	
Amylase (IU/l)	<4000	158	41	0.001
	≥4000	151	73	
Bilirubin (μmol/l)	<25	155	45	0.001
	≥25	139	73	

one episode, one patient had evidence of viral infection on sequential serological investigation, in 56 episodes a single etiological factor was not identified after investigation (these include patients with pancreatitis after cholecystectomy and patients who denied excessive alcohol intake although this appeared clinically to be the etiological factor), and 34 had insufficient investigation to identify the etiology. Seventeen (18%) of these 93 episodes proved fatal within the same hospital admission. The overall mortality for the Group A patients was 10.6%.

Seven of the 14 factors tested showed significant differences in value between the gallstone and alcohol groups (Table 1). The factor which differed the most between the two groups was serum alkaline phosphatase. Mean serum alkaline phosphatase concentration in gallstone-associated pancreatitis was 547 ± SEM 27 IU/l, and in alcohol-associated pancreatitis 263 ± SEM 26 IU/l. For the gallstone group, the median alkaline phosphatase level was 437 IU/l and the alcohol group was 220 IU/l. A cutoff level of 300 IU/l was used for chi square testing. If alkaline phosphatase was ≥ 300 IU/l, 86% of episodes were gallstone-associated, and if <300 IU/l, then only 28% (p < 0.001). Similarly age ≥ 50 years, ALT ≥ 100 IU/l, female sex, AST ≥ 100 IU/l, amylase ≥ 4000 IU/l, and bilirubin ≥ 25 μmol/l were each significantly (all p < 0.001) associated with the presence of gallstones (Table 1).

Stepwise logistic regression showed that five of these factors had independent significance in predicting gallstones. The five factors were: alkaline phosphatase ≥ 300 IU/l, age ≥ 50 years, ALT ≥ 100 IU/l, female sex, and amylase ≥ 4000 IU/l. There were 290 episodes in which complete information was available on all five factors. This method of analysis generates a probability for gallstones vs. alcohol as the etiological factor for each par-

TABLE 2. Patterns of Predictive Factors and Computed Probability of Gallstone Etiology in 290 Episodes of Acute Pancreatitis, Based on Logistic Regression Analysis in Group A

Sex (F = +)	Age (≥50 = +)	Amylase (≥4000 = +)	ALT (≥100 = +)	Alk. Phos. (≥300 = +)	Probability of Gallstones	No. of Episodes	
						Gallstones	Alcohol
-	-	-	-	-	0.02	2	41
-	-	-	-	+	0.08	0	6
-	-	-	+	-	0.10	0	3
-	-	-	+	+	0.34	0	1
-	-	+	-	-	0.06	0	17
-	-	+	-	+	0.24	0	0
-	-	+	+	-	0.29	1	4
-	-	+	+	+	0.66	4	1
-	+	-	-	-	0.19	0	9
-	+	-	-	+	0.52	5	1
-	+	-	+	-	0.58	0	1
-	+	-	+	+	0.87	7	1
-	+	+	-	-	0.46	8	6
-	+	+	-	+	0.80	2	1
-	+	+	+	-	0.84	1	0
-	+	+	+	+	0.96	18	1
+	-	-	-	-	0.16	2	13
+	-	-	-	+	0.48	4	2
+	-	-	+	-	0.54	1	0
+	-	-	+	+	0.85	5	1
+	-	+	-	-	0.42	2	5
+	-	+	-	+	0.77	2	1
+	-	+	+	-	0.81	1	0
+	-	+	+	+	0.95	16	0
+	+	-	-	-	0.72	5	1
+	+	-	-	+	0.92	11	2
+	+	-	+	-	0.94	5	0
+	+	-	+	+	0.99	17	1
+	+	+	-	-	0.90	8	0
+	+	+	-	+	0.98	4	1
+	+	+	+	-	0.98	4	0
+	+	+	+	+	0.996	35	0
						170	120

ticular combination of predictive factors, positive or negative (Table 2). Using the probability table, if gallstones are selected as the likely etiological factor when the probability is >0.5 , and alcohol when the probability is <0.5 , then separation between the groups is correct for 89% of episodes. Gallstones were present in 92% of episodes in which the probability is >0.5 , and 89% of episodes associated with gallstones have a predicted probability >0.5 . Separation between the two etiological groups was not improved by multivariate analysis which used actual val-

ues of each of these five factors rather than the high/low separation described. The high/low method has the advantage of simplicity.

By using the same five predictive factors as the basis of a simple scoring system (Table 3), it was found that in the group of patients with zero or one factor present, 89 episodes were associated with alcohol and four with gallstones. The group of patients with two factors positive had 26 episodes with gallstone-pancreatitis and 21 episodes with alcohol-pancreatitis. The presence of three or more positive factors defined a group of patients in which 140 episodes were associated with gallstones and only 10 with alcohol.

TABLE 3. Assessment of a Simple Scoring System to Separate Gallstone and Alcohol Etiologies in Acute Pancreatitis in Group A

No. of Positive Factors	No. of Episodes	Per Cent Gallstone	Per Cent Alcohol
0	43	5	95
1	50	4	96
2	47	55	45
3	53	86	14
4	62	95	5
5	35	100	0

Group B Patients

Of the 59 patients in Group B, two patients experienced two episodes of acute pancreatitis, providing 61 episodes for analysis. Five episodes occurred in patients who had previously had cholecystectomy and an etiological factor has been identified in all remaining patients. The re-

maining 56 patients had gallstones confirmed or satisfactorily excluded by imaging, surgery, or autopsy. Thirty-one patients were demonstrated to have gallstones.

Using the probability table generated from the Group A patients and the criterion that the presence of gallstones is predicted by a theoretical probability of greater than 0.5, the presence or absence of gallstones was correctly predicted in 50 episodes (89.3%) of acute pancreatitis (Table 4). Three patients in whom gallstones were incorrectly predicted had both negative ultrasound and negative oral cholecystography. One of these was a 15-year-old girl with a family history of acute pancreatitis who developed recurrent episodes without any identified etiological agent. Three patients, who were predicted as not having gallstones, in fact had them demonstrated, one at operation, one on oral cholecystography and ultrasound, and one on ultrasound alone.

Using the scoring system, when there were less than two factors positive, 18 episodes were correctly predicted as not associated with gallstones and one incorrectly. When there were more than two factors positive, 25 patients were correctly predicted as having gallstones and three (one the 15-year-old girl already described) were incorrectly predicted as having gallstones (Table 5).

Discussion

The reliable demonstration of the presence or absence of gallstones remains an elusive goal, particularly in the presence of acute pancreatitis. Imaging methods remain the diagnostic mainstays for the exclusion of gallstones and are most accurate when performed after the acute episode has settled. Many patients in whom gallstones are demonstrated proceed eventually to surgical confirmation, but the absence of gallstones at surgery or autopsy cannot exclude the small possibility that the passage of a solitary or last gallstone has caused acute pancreatitis, although gallstones which cause pancreatitis tend to be multiple.¹⁶ In spite of such difficulties, these methods remain the yardstick by which we judge the presence or absence of gallstones.

Imaging methods of identifying gallstones early in an episode of acute pancreatitis have had variable success. In a trial at this hospital, 26 of 62 patients subsequently shown to have gallstones did not have them demonstrated by ultrasound within 1 week of admission.⁹ This was often because the gallbladder was not adequately visualized. It is well recognized that the radiological investigation of the biliary tract may prove negative in the presence of gallstone-associated pancreatitis^{11,12}, and may be abnormal in the presence of alcohol-associated pancreatitis.^{8,10} The role of radionuclide scanning as an early diagnostic tool in patients with acute pancreatitis remains in dispute.^{4,17,18}

TABLE 4. *Prospective Use of Prediction by Computed Probability*

	Gallstone	No Gallstone	Total
p < 0.5	3	22	25
p > 0.5	28	3	31
Total	31	25	56

Previous nonimaging methods for detecting gallstones in acute pancreatitis have used gallstone- and alcohol-associated pancreatitis as the basis for analysis, because these provide the two largest etiological groups. We have also used these groups for the initial statistical analysis but have confirmed the validity of the predictive methods on all patients with sufficient data available, not only the gallstone- and alcohol-associated groups. Computer analysis based on clinical features was demonstrated by Graham and Wyllie¹⁹ to have an accuracy of 92% in their patients, but this method has not been as accurate when tested by other groups.^{9,17} Previous efforts at diagnosis based on biochemical features^{17,20-22} have demonstrated that alkaline phosphatase, ALT, serum bilirubin, and serum amylase all have value in predicting gallstones.

In our series, not only these biochemical features but also age and sex were significant factors in predicting gallstones. The simple progression to a combination of these factors has enabled us to increase the predictive accuracy to 89% when separating the gallstone and alcohol etiological groups, although it must be stressed that the analysis was not applied to 23% of episodes which did not fit into these two major diagnostic groups. When tested prospectively on all patients with acute pancreatitis without previous cholecystectomy, the probability method was able to identify a group of patients, 90% of whom had gallstones while 88% of the remaining patients had gallstones satisfactorily excluded. The scoring method, when applied to these 56 admissions correctly, predicted the presence or absence of gallstones in 43 (77%), incorrectly predicted four (7%), and made no prediction in nine (16%). We accept that this estimate of accuracy relies on established methods of imaging which are themselves not wholly reliable in detecting gallstones in the early stages after admission with gallstone-associated pancre-

TABLE 5. *Prospective Use of Prediction by Scoring*

No. of Positive Factors	Gallstone	No Gallstone	Total
0	0	10	10
1	1	8	9
2	5	4	9
3	9	2	11
4	7	1	8
5	9	0	9
Total	31	25	56

atitis. However, the final diagnosis derived for patients in this series depends on results of imaging not restricted to the early period, as well as on the findings at surgery and autopsy.

The case for immediate surgery in gallstone associated acute pancreatitis has been advocated by Acosta, et al.³ who reported a reduction in mortality, from 16% in a retrospective series, to 2% on the introduction of a policy of surgery within 48 hours of admission. They found that this timing led to the discovery of stones impacted in the ampulla of Vater in 33 of 46 patients having immediate surgery. Stone, et al.⁴, in a randomized study of 65 patients, compared the results of immediate surgery (undertaken within 73 hours of admission) with delayed surgery at 3 months and showed no significant difference in mortality, major morbidity, or duration of initial admission but pointed out that immediate surgery avoided the second admission for elective surgery.

When Ranson⁵ reviewed patients having early surgery (within 1 week of admission) and nonoperative treatment of gallstone associated pancreatitis, he reported a significantly higher mortality for early surgery (23% compared with 0%) and that this increased mortality occurred mainly in patients with severe pancreatitis. Other investigators reviewing the results of surgery have reported higher mortality with early surgery^{23,24} but have included patients selected for early surgery because of failure of conservative therapy. Osborne et al.⁶ reported a particularly high mortality (50%) in patients who failed to settle on conservative therapy and then proceeded to surgery, but no mortality in patients who settled and proceeded to operation at the same admission.

Kelly²⁵ has reported a higher mortality with immediate surgery (12%) than early surgery performed between 5 and 7 days (0%), and late elective surgery at a further admission (7%). He also reported a high incidence of impacted stones (63%) in patients having immediate surgery. The role of immediate surgery remains unclear and early endoscopic papillotomy, as described by Safrany and Cotton⁷ requires further assessment and may have a role in the management of gallstone associated acute pancreatitis.

The natural reluctance of surgeons to rely on a predictive index rather than an imaging technique in detection of gallstones may mean that the system will be applied to the selection of patients for more intensive investigation by methods such as ERCP, although the role of this technique and that of endoscopic papillotomy are as yet uncertain in the present context. The advantage of our predictive method lies in its simplicity. The information required can be obtained at routine biochemical screening in many hospitals, and all three biochemical tests are

already frequently carried out in the first few hours of admission of most patients with acute pancreatitis.

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