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*Original article*

# Clinical discrimination between choledocholithiasis and biliopancreatic malignancy based on a new biochemical model

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## SUMMARY

**Purpose: This study aims to establish predictive laboratory tests, which could confidently assist for an initial clinical discrimination of choledocholithiasis from biliopancreatic malignancy, before an invasive endoscopic or surgical diagnosis. Results: A total of 174 patients, who underwent ERCP were analyzed. Patients with final diagnosis of choledocholithiasis (137 patients) and biliopancreatic adenocarcinoma (37 patients) had their biochemistry parameters compared using Mann-Whittney test. Cut-off values for each parameter were defined. The cut-off values that provided the best trade-off between sensitivity and specificity were: 8.65 mg/dL for total bilirubin, 276 U/L for serum alkaline phosphatase and 306 IU/ml for CA19-9. A patient most probably (96%) suffers from cancer, if he has high incriminating values in all these three parameters. Conclusions: A simple, reproducible, easy-to-obtain predictive model with laboratory tests, successfully differentiates choledocholithiasis from malignant biliopancreatic diseases and could be useful for a more cost-effective investigation and treatment of patients with such pathology.**

**Key words:** pancreatic cancer; cholangiocarcinoma; choledocholithiasis; biochemistry tests; endoscopic retrograde cholangiopancreatography; CA19-9.

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## INTRODUCTION

Differential diagnosis between malignant and benign biliopancreatic diseases is not always easy, even with invasive diagnostic tools, such as endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasonography with fine needle aspiration or laparoscopic surgery. In some cases the clinical presentation of pancreatic carcinoma is similar to that of several benign diseases.[1] Therefore it is highly important to be able to accurately differentiate extrahepatic cholestasis due to biliopancreatic malignancy from that caused by benign diseases such as common bile duct stones (CBDS) by using cost and time-saving means. These conditions deserve subsequent management including the need for therapeutic ERCP and/or surgical techniques, which require specific skills and materials. Patients could benefit from an optimal combination of currently available therapeutic means.

There are several published studies[2,3] concerning the use of noninvasive (routine laboratory) tests in predicting the presence of CBDS and the use of tumor markers in malignant obstructive jaundice.[1,4] Numerous efforts have been

***Abbreviations***

*CBDS common bile duct stones*
*ERCP=endoscopic retrograde cholangiopancreatography;*
*US=ultrasonography;*
*AST=aspartate aminotransferase;*
*ALT=alanine aminotransferase;*
*SAP=serum alkaline phosphatase;*
*γGT=γ-glutamyl transferase;*
*tB/dB=total/direct bilirubin;*
*CEA=carcinoembryonic antigen;*
*CA19-9=carbohydrate antigen 19-9;*
*ROC=receiver operating characteristics;*
*HIV=human immunodeficiency virus*

made in the past to define predictive criteria as well as predictive scores for choledocholithiasis, but no straightforward conclusions were evident[5]. In addition, elevated serum tumor markers {carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), carbohydrate antigen 125, a-fetoprotein} were observed in both benign and malignant biliopancreatic diseases with obstructive jaundice. [1,4]

For these reasons this study aims to establish predictive factors based on non-invasive, widespread, inexpensive and rapidly available tests which could assist physicians to make confidently an initial differentiation of CBDS from malignancy.

## METHODS

### *Patients selection and diagnosis*

A total of 410 consecutive Caucasian patients were studied prospectively. They were consider to suffer from biliopancreatic disease judging from their clinical presentation. The following elements were studied on admission: age, sex, clinical symptoms and signs (pain, fever, jaundice), routine blood and urine laboratory tests [complete blood count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum alkaline phosphatase (SAP), γ-glutamyl transferase (γGT), total/direct bilirubin (tB/dB), serum and urine amylase, tumor markers: CEA, CA19-9, a-fetoprotein], as well as ultrasonography (US) of the upper abdomen. All demographic, medical history, clinical and laboratory information were prospectively entered in a registry database. Blood and urine laboratory parameters were studied as potential predictive factors for the discrimination of choledocholithiasis from biliopancreatic malignancy.

Two hundred thirty six patients were excluded because of the following exclusion criteria: liver (hepatocellular) malignancy (primary or metastatic), chronic or concurrent liver disease, biliary injury or stricture, primary sclerosing cholangitis, choledochocele, congenital hepatobiliary abnormalities, chronic pancreatitis, Billroth II gastrectomy, previous endoscopic sphincterotomy or stent placement, sphincter of Oddi adenoma or carcinoma, sphincter of Oddi dyskinesia (known or subsequently proved) and HIV infection.

Finally, 174 patients were eligible to enter the study according to the following inclusion criteria: presence of symptoms (biliary pain syndrome with or without fever, jaundice), and/or abnormal laboratory tests (at least one of the above mentioned blood and urine tests over the upper limits of normal) together with an abnormal US (mandatory). The latter was considered abnormal if it included findings such as the presence of an hyperechoic image in the bile duct lumen (i.e. stone), a dilated common bile duct (CBD) (measured in its mid portion > 6mm in diameter with the gallbladder in situ or >9mm with previous cholecystectomy) [3,6] and a mass-lesion revealed in the biliopancreatic region.

ERCP was performed with a standard side viewing duedenoscope (Olympus Optical Co., Tokyo, Japan) by four experienced Consultant Gastroenterologists. An informed written consent was obtained from all patients prior to ERCP in accordance with our institutional Review Board. The average time span between laboratory tests and ERCP was 3 days. Spiral computed tomography was performed within 48 hours from admission in all patients with suspected malignancy in the biliopancreatic region (presented with painless jaundice, excessive weight loss and/or a pathologic lesion or mass revealed in physical examination or US) or suspected but not proved choledocholithiasis. Computed tomography was not performed in cases of evident lithiasis of the common bile duct without any other lesion shown in the ultrasound.

The final diagnosis was achieved by examining the cholangiopancreatography films by two blinded gastroenterologists experienced in ERCP, the endoscopist clinical opinion when needed (e.g. the visible extraction of stones or sludge) and the positive histology or cytology result for malignancy. In cases in which, despite the clinical and imaging suspicion, the results of cytology or histology were negative or undetermined, an endoscopic US with fine needle aspiration was performed.

Patients were divided in two groups according to the final diagnosis: Group A comprised 137 patients with CBDS or luminal sludge. Group B comprised 28 patients with pancreatic adenocarcinoma and 9 patients with cholangiocarcinoma both verified either by histological or cytological examination.

All patients were followed-up for up to 6 months in order to confirm the diagnosis.

### *Statistical Analysis*

The distribution of the clinical presentation of the patients among the two study groups was investigated with the $\chi^2$ test. The biochemistry markers of the two groups were compared with the Mann-Whitney test. Parameters, which were found to be significantly different between the two groups, were further investigated using receiver operating characteristics curves (ROC), which allow for the calculation of their discrimination ability. The methodology

provides the means to estimate the cut-off value for each parameter that yields the best trade-off between sensitivity and specificity.[7,8] On the basis of the optimal cut-off values new variables are formed, which follow the binary distribution, i.e. they indicate whether each subject's value for the specific parameter is either above or below the cut-off point. The 2X2 contingency tables formed by the frequency distribution of these new variables across the two groups allow the estimation of a number of useful measures (sensitivity and specificity, positive and negative likelihood ratios and predictive values, as well as the risk and odds ratios with their 95% confidence intervals). Finally, in search for the combination of parameters that provides the best diagnostic test discriminating the cancer group from the lithiasis group, a stepwise logistic regression method and a simple agglomerative model were employed.

## RESULTS

Of the 174 patients in this study, 113 (65%) were women. The mean age was 67.9±14.2 years (range 24-92 years) and 84 (48%) of the patients were older than 70 years. The lithiasis group was 137/174 patients (79%) and the cancer group 37/174 patients (21%). Of the 137 patients with lithiasis, 96 (70%) had CBDS $\leq$1cm and 41 (30%) had CBDS > 1cm in diameter. The symptoms and other relevant parameters of patients' clinical presentation are depicted in Table 1.

It is quite clear from table 1 that the clinical presentation of the two groups is quite distinct ($\chi^2$=126, d.f.=6, p<0.001). The majority of the patients, who were later diagnosed with biliopancreatic cancer, were admitted to the hospital with painless jaundice.

Table 2 shows the median values and the interquartile ranges of the two groups for the biochemistry markers under investigation. The Mann-Whitney test confirmed statistically significant differences between the groups for total and direct bilirubin, SAP, CA19-9, γGT and white blood cells at the 0.01 level and for hematocrit and AST at the 0.05 level.

For all the above parameters ROC curves were constructed in order to evaluate their discrimination ability. It was found that for total and direct bilirubin, SAP, CA19-9 the discrimination ability was above 0.800, which is expressed in this case by the area under the curve (Figure 1). This means that these four parameters discriminate the two groups fairly well.

For each parameter the cut-off value that provides the best trade-off between sensitivity and specificity was found. These values are 8.65 mg/dL for total bilirubin (8.6 fold the normal), 3.85 mg/dL for direct bilirubin (7.5 fold the normal), 276 U/L for SAP (2.2 fold the normal) and 306 IU/ml for CA19-9 (8.3 fold the normal). The corresponding sensitivities, specificities, positive and negative likelihood ratios and predictive values, risk and odds ratios and total percentages of correctly classified cases are depicted in Table 3.

The above cut-off values were used to create four new variables, corresponding to the four parameters under consideration, but with a binary distribution. These four new binary variables were entered as the independent variables in a stepwise binary logistic regression model with the two subgroups of lithiasis and cancer being the binary dependent variable.

Two points are notable: firstly that direct bilirubin does

**Table 1** Clinical characteristics and presentation of study patients.

| | **Final Diagnosis** | |
|---|---|---|
| | **CBD Lithiasis** | **Biliopancreatic Cancer** |
| No of patients | 137 | 37 |
| Male/female ratio (patients) | 49/88 | 12/25 |
| Median age-yrs (interquartile range) | 70 (15) | 71(20) |
| Biliary colic | 53 (38.7%) | 0 (0%) |
| Cholangitis | 38 (27.5%) | 0 (0%) |
| Painful jaundice | 26 (19.0%) | 6 (16.2%) |
| Painless jaundice | 2 (1.5%) | 29 (78.4%) |
| Acute pancreatitis | 13 (9.5%) | 0 (0%) |
| Asymptomatic / Increase of LFT's* | 4 (2.9%) | 2 (5.4%) |
| Asymptomatic / Normal LFT's | 1 (0.7%) | 0 (0%) |

* *LFT's: liver function tests*

**Table 2** Descriptive statistics of biochemistry markers [median (interquartile range)] and their comparisons between the two groups with the Mann-Whitney test.

| | CBD Lithiasis | Biliopancreatic Cancer | p-value |
|---|---|---|---|
| t-Bilirubin (mg/dL) | 2.6 (4.3) | 13.1 (9.3) | <0.001 |
| d-Bilirubin (mg/dL) | 1.4 (3.0) | 8.2 (6.3) | <0.001 |
| SAP (U/L) | 193 (187) | 509 (463) | <0.001 |
| CA19-9 (U/mL) | 41 (186) | 424 (1202) | <0.001 |
| γGT (U/L) | 356 (417) | 636 (580) | <0.001 |
| AST (IU/L) | 91 (157) | 135 (132) | <0.027 |
| ALT (IU/L) | 155 (259) | 188 (327) | 0.115 |
| AFP a (U/mL) | 4.1 (3.0) | 2.8 (2.3) | 0.287 |
| CEA (ng/mL) | 2.2 (2.4) | 4.9 (12.8) | 0.142 |
| HEMATOCRIT (%) | 40.0 (5.6) | 37.5 (6.9) | 0.014 |
| HEMOGLOBIN (g/dL) | 13.0 (2.0) | 12.5 (2.8) | 0.074 |
| WBC b (103/μL) | 7600 (3816) | 6950 (1498) | <0.001 |
| AMYLASE SERUM (U/mL) | 56 (62) | 50 (56) | 0.186 |
| AMYLASE URINE (U/mL) | 478 (1627) | 219 (1349) | 0.345 |

*a a-fetoprotein, b White Blood Cells*

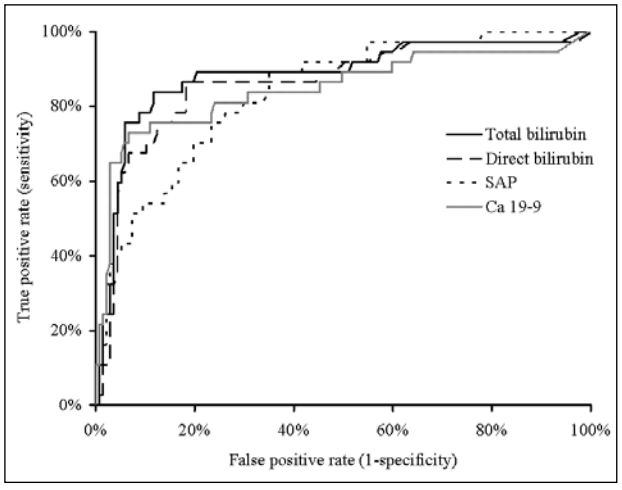


**Figure 1** ROC curves for total and direct Bilirubin, SAP and CA19-9.

not meet the criteria to enter the regression equation. This is not indicative against its discrimination ability, but rather of its strong correlation with total bilirubin (r=0.783). All the discrimination information inherent in direct bilirubin was already provided by total bilirubin. The results of the regression model are shown in table 4.

Secondly, the entrance of the other three parameters in the regression equation indicates that each parameter provides complementary diagnostic information. This is also confirmed by the fact that total bilirubin, SAP and CA19-9 do not have high Pearson's correlation coefficients between each other. These correlation coefficients are 0.342 for total bilirubin and SAP, 0.531 for total bilirubin and CA19-9 and 0.130 for SAP and CA19-9.

The above results can be better understood and, what is more important, better employed in practice, by the frequency distribution shown in Table 5. If we take the three risk factors under consideration (tB, SAP and CA19-9) in their binary form with the given cut-off values, then each patient can be characterized by a risk value (score) ranging from 0 to 3. A risk value of 0 means that the patient's values for the three parameters are below the corresponding cut-off values. At the other end a risk value of 3 means that all three of the patient's values are above the cut-off points. It was found that 121 patients from a total of 127 patients with score ≤1 suffered from choledocholithiasis (96%). Similarly, 23 patients from 24 patients with score 3 were finally diagnosed with biliopancreatic cancer (96%). Using score 1 as the discrimination limit, 126 patients were found with score ≤1 and most probably suffered from lithiasis and 48 were found with score >1 and probably suffered from cancer. Taking this limit under consideration, the discrimination ability of the model was 88% (153/174 patients). Statistically, the regression model was able to correctly classify 91.4% of the cases.

## DISCUSSION

The invention and development of new medical technologies, concerning the biliopancreatic diseases, (ther-

**Table 3** Discrimination ability and best cut-off values for the four biochemistry markers derived from the ROC curves. Statistical measures derived from the resulting 2X2 contingency tables of positive and negative values of the markers against the appearance of cancer or lithiasis.

| Statistical measure | t-Bilirubin | d-Bilirubin | SAP | CA19-9 |
|---|---|---|---|---|
| Discrimination ability | 0.885 | 0.863 | 0.838 | 0.868 |
| 95% confidence interval | 0.814-0.956 | 0.789-0.937 | 0.769-0.907 | 0.762-0.934 |
| Cut-off value | 8.65 mg/dL | 3.85 mg/dL | 276 U/L | 306 U/mL |
| TP | 31 | 32 | 33 | 27 |
| FP | 15 | 25 | 48 | 15 |
| TN | 122 | 112 | 89 | 122 |
| FN | 6 | 5 | 4 | 10 |
| Sensitivity | 0.838 | 0.865 | 0.892 | 0.730 |
| Specificity | 0.891 | 0.818 | 0.650 | 0.891 |
| LR+ | 7.65 | 4.74 | 2.55 | 6.66 |
| LR- | 0.18 | 0.17 | 0.17 | 0.30 |
| Positive PV | 0.67 | 0.56 | 0.41 | 0.64 |
| Negative PV | 0.95 | 0.96 | 0.96 | 0.92 |
| Risk ratio | 14.4 | 13.1 | 9.5 | 8.5 |
| 95% confidence interval | 6.0-34.5 | 5.4-31.9 | 3.5-25.6 | 4.5-16.0 |
| Odds ratio | 42 | 28.7 | 15.3 | 22 |
| 95% confidence interval | 15.1-117.2 | 10.2-80.9 | 5.1-45.7 | 8.9-54.1 |
| % correctly classified | 0.879 | 0.828 | 0.701 | 0.856 |

*TP: True Positive, FP: False Positive, TN: True Negative, FN: False Negative,*
*LR+: Positive Likelihood Ratio, LR-: Negative Likelihood Ratio, PV: Predictive Value*

**Table 4** Results of the stepwise logistic regression model with group (lithiasis and cancer) as the dependent variable and the three parameters (total bilirubin, SAP and CA19-9) in their binary form as the predictors.

| Steps | Variables in the equation | Exp(B) (Odds ratio) | 95.0% C.I. Lower | Upper |
|---|---|---|---|---|
| 1 | t-bilirubin | 42.0 | 15.1 | 117.2 |
| 2 | t-bilirubin | 36.1 | 11.7 | 111.8 |
| | SAP | 12.4 | 3.4 | 45.3 |
| 3 | t-bilirubin | 13.7 | 3.8 | 48.9 |
| | SAP | 19.8 | 4.5 | 87.4 |
| | CA19-9 | 7.5 | 2.0 | 28.7 |

apeutic ERCP, endoscopic US, laparoscopic extraction of CBDS, etc.) offers new and expensive diagnostic and therapeutic options for these diseases. These options often coexist with an increasing cut down of financial resources from health insurance systems. The optimal distribution of these scarce resources in a rational way means that expensive technologies should be used for diagnosis and treatment only to improve patient's care in a cost-effective way. This problem strengthens the interest in low-cost, non-invasive, rapidly available diagnostic tests for biliopancreatic diseases. Some authors have already address this issue, as recently by Nathan T. et al in which a model was developed for the prediction of performing

**Table 5** Differential diagnosis of choledocholithiasis vs malignant disease using total Bilirubin, SAP and CA19-9.

| | Number of risk factors present (score) | | | | Total (patients) |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | |
| Lithiasis (patients) | 76 | 45 | 15 | 1 | 137 |
| Cancer (patients) | 1 | 4 | 9 | 23 | 37 |
| Total (patients) | 77 | 49 | 24 | 24 | 174 |
| Discrimination ability | 96% (lithiasis) | 92% (lithiasis) | 37% (cancer) | 96% (cancer) | |

therapeutic ERCP, based on age, gender, serum amylase, serum liver tests and US.[9,10]

Differential diagnosis of benign biliopancreatic diseases (such as choledocholithiasis) vs. malignancy (pancreatic cancer and cholangiocarcinoma) is in several cases difficult and this may be due to the overlap of symptoms. More complicated cases, such as the presence of repeated normal serum liver enzymes together with CBDS, are very uncommon (0-5%).[11-14] In this cohort only one patient (0.7%) suffering from CBDS was found with normal liver enzymes.

There are many studies in the literature that discuss predictive biochemistry markers for the diagnosis of the presence of CBDS[2,3,5,9,10,15,16] or the pancreatic and biliary malignancy.[1,4,17-28] However, these studies have separately examined the predictive factors for the respective diseases. Moreover, their results are extremely variable and conflicting without any consensus.[1-3] In the present study, patients were selected and analyzed by means of the common medical practice offering an algorithm for the early differential diagnosis between choledocholithiasis and malignant biliopancreatic diseases. The sensitivity (73%) and specificity (89%) of serum CA19-9 in detecting pancreatic cancer that was presently found (Table 3), were within the limits of variation reported previously (68-92% and 44-97% respectively).[1,4] Similarly, sensitivity (84%), specificity (89%), positive predictive value (67%), negative predictive value (95%), positive likelihood ratio (7.65) and negative likelihood ratio (0.18) of total bilirubin in detecting lithiasis of CBD of the current study (Table 3) were comparable with the limits of variation reported previously (69–74%, 48–92%, 31–57%, 66–99%, 4.8 and 0.54 respectively).[5,6,9,29,30] The study has demonstrated three parameters (tB, SAP and CA19-9) able to discriminate correctly the majority (88%) of the cases concerning choledocholithiasis vs. malignancy. Furthermore, the present findings demonstrate that no single predictive factor is completely accurate in differentiating CBDS from biliopancreatic cancer and are in accordance with previous studies.[15-17] Each of the three risk factors provides complementary information on the differential diagnosis. Based on the classification of patients (Table 4), there are three significant observations to be stated. Firstly, a patient most probably (96%) has a cancer if he has high incriminating values in all three parameters {tB (8.6 fold the normal), SAP (2.2 fold the normal) and CA19-9 (8.3 fold the normal)} under consideration. Secondly, it is highly unlikely (4%) that a patient with lithiasis (CBDS) will have values above the cut-off point in all three parameters. Finally, it is likewise unlikely that a patient with cancer will not be characterized by at least one predictive factor above the cut-off value. In practice, patients with score 0 or 1 and score 3, most probably (96%) may have a correct clinical diagnosis using this model (table 5).

The study's objective was to create a model of laboratory tests (tB – SAP – CA19-9) that is easy to use, based on universally, not costly and rapidly available data, differentiating choledocholithiasis from cancer in the biliopancreatic region, and in this way helpful to patients' management schedules.

Hyperamylasemia was not a significant predictor of CBDS and biliopancreatic cancer.[4] This finding is concordant with other studies, where hyperamylasemia may be best used as a predictor of recurrent pancreatitis rather than as a predictor of CBDS or cancer discovery. Moreover increased serum amylase may lower the predictive accuracy of other tests.[4,31,32]

Management strategies, especially in the primary and secondary health care level, may be enriched by diagnostic algorithms based on predictive clinical and laboratory information. This model may help for the initial discrimination of choledocholithiasis from cancer in the biliopancreatic region. If the three predictors (tB, SAP and CA19-9) are present (above their cut-off limits–score=3), a therapeutic strategy could readily be adopted towards biliopancreatic malignancy (a fully surgical treatment, operable or not cancer and therapeutic ERCP). On the other hand, the absence of the three predictors (score=0) is strongly suggestive for CBDS and the patient could be transferred to a hospital which provides access to therapeutic techniques and experienced practitioners for applying endoscopic US and endoscopic sphincterotomy. The model can not be applied in patients with negative Lewis blood type who are unable to express CA19-9 (approximately 10% of Caucasians).[18] Also, in intermediate cases (score 2) a thorough search for the exclusion of malignancy should be followed. Advanced imaging studies (spiral computed tomography or magnetic resonance) and an accurate but minimally invasive diagnostic method, such as endoscopic US (with or without fine needle aspiration), could be applied. It has been shown that performing endoscopic US prior to therapy had no significant impact on cost-effectiveness in patients with high risk of CBDS[33] but was strongly cost-effective in patients with an intermediate risk.[34] Endoscopic US is helpful in the investigation of the biliopancreatic diseases, but an advanced endoscopical technology, specialization and experience is needed and it is not available in any hospital.

In conclusion, this study shows that a simple screening of patients at risk for biliopancreatic malignancy or cho-

ledocholithiasis could be achieved with three non-invasive, widespread, inexpensive and rapidly available laboratory predictive criteria (tests), irrespective to the patient's age. Thus, this model should be prospectively evaluated in a primary or secondary care level where it may be more applicable. It is obvious that in this case hospital and financial resources can be allocated more expediently. Moreover, the patient can be diagnosed and treated in a more cost-effective and safe way, achieving lower complications rate.

## REFERENCES


1. Hyöty M, Hyöty H, Aaran RK, Airo I, Nordback I: Tumor antigens Ca195 and Ca19-9 in pancreatic juice and serum for the diagnosis of pancreatic carcinoma. Eur J Surg 1992; 158:173-179.
2. Roston AD, Jacobson IM: Evaluation of the pattern of liver tests and yield of cholangiography in symptomatic choledocholithiasis: a prospective study. Gastrointest Endosc 1997; 45:394-399.
3. Prat F, Meduri B, Ducot B, Chiche R, Salimbeni-Bartolini, R, Pelletier G: Prediction of common bile duct stones by non invasive tests. Ann Surg 1999; 229:362-368
4. Nazli O, Bozdag AD, Tansung T, Kir R, Kaymak E: The diagnostic importance of CEA and CA 19-9 for the early diagnosis of pancreatic carcinoma. Hepato-Gastroenterology 2000; 47:1750-1752
5. Abboud PA, Malet PF, Berlin JA, Staroscik R, Cabana MD, Clarke JR, Shea JA, Schwartz JS, Williams SV: Predictors of common bile duct stones prior to cholecystectomy: a meta-analysis. Gastrointest Endosc 1996; 44:450-459
6. Barkun AN, Barkun JS, Fried GM, Ghitulescu G, Steinmetz O, Pham C, Meakins J, Goresky C, McGill Gallstone Treatment Group: Useful predictors of bile duct stones in patients undergoing laparoscopic cholecystectomy. Ann Surg 1994; 220:32-39
7. Hanley JA: Receiver Operating Characteristic (ROC) methodology. Critic Rev Diagnost Radiol 1989; 29:307-335
8. Schouw YT, Straatman H, Verbeek AL: ROC curves and the areas under them for dichotomized tests: empirical findings for logistically and normally distributed diagnostic test results. Med Decis Making 1994; 14:374–381
9. Nathan T, Kjeldsen J, Schaffalitzky de Muckadell OB: Prediction of therapy in primary endoscopic retrograde cholangiopancreatography. Endoscopy 2004; 36:527-534
10. Wang CH, Mo LR, Lin RC, Kuo JY, Chang KK: Rapid diagnosis of choledocholithiasis using biochemistry tests in patients undergoing laparoscopic cholecystectomy. Hepato-Gastroenterology 2001; 48:619-621
11. Kama NA, Atli M, Doganay M, Kologlu M, Reis E, Dolapci M: Practical recommendations for the prediction and management of common bile duct stones in patients with gallstones. Surg Endosc 2001; 15:942-945
12. Pereira-Lima JC, Jacobs R, Busnello JV, Benz C, Blaya C, Riemann JF l: The role of serum liver enzymes in the diagnosis of choledocholithiasis. Hepato-Gastroenterology 2000; 47:1522-1525
13. Goldman DE, Gholson CF: Choledocholithiasis in patients with normal serum liver enzymes. Dig Dis Sci 1995; 40:1065-1068
14. Houdart R, Perniceni T, Darne B, Salmeron M, Simon JF: Predicting common bile duct lithiasis: Determination and prospective validation of a model predicting low risk. Am J Surg 1995; 170:38-43
15. Pasanen P, Pikkarainen P, Alhava E, Partanen K, Pentilla I: Value of serum alkaline phosphatase, aminotransferases, gamma-glytamyl transferase, leucine aminopeptidase, and bilirubin in the distinction between benign and malignant diseases causing jaundice and cholestasis: results from a prospective study. Scand J Clin Lab Invest 1993; 53:35-39
16. Al-Mofleh IA, Aljebreen AM, Al-Amri SM, Al-Rashed RS, Al-Faleh FZ, Al-Freihi HM. Abdo AA, Isnani AC: Biochemical and radiological predictors of malignant biliary strictures. World J Gastroenterol 2004; 10:1504-1507
17. Mann DV, Edwards R, Ho S, Lau WY, Glazer G: Elevated tumour marker CA19-9: clinical interpretation and influence of obstructive jaundice. Eur J Surg Oncol 2000; 26:474-479
18. Rosen A, Linder S, Harmenberg U, Regert S: Serum levels of CA19-9 and CA50 in relation to Lewis blood cell status in patients with malignant and benign pancreatic disease. Pancreas 1993; 8:160-165
19. Willett GC, Daly GW, Warshaw LA: CA19-9 is an index of response to neoadjunctive chemoradiation therapy in pancreatic cancer. Am J Surg 1996; 172:350-352
20. Bain VG, Abraham N, Jhangri JS, Alexander TW, Henning RC, Hoskinson ME, Maguire CG, Lalor EA, Sadowski DC: Prospective study of biliary strictures to determine the prediction of malignancy. Can J Gastroenterol 2000; 14:397-402
21. Plebani M, Basso D, Panozzo MP, Fogar P, Del Favero G, Naccarato K: Tumor markers in the diagnosis, monitoring and therapy of pancreatic cancer: state of the art. Int J Biol Markers 1995; 10:189-199
22. Buffet C, Fourre C, Altman C, Prat F, Fritsch J, Choury A, Briantais M-J, Desgrez A, Etienne J-P: Bile levels of carcino-embryonic antigen in patients with hepatopancreatobiliary disease. Eur J Gastroenterol Hepatol 1996; 8:131-134
23. Bose SM, Mazumdar A, Prakash VS, Kocher R, Katariya S: Evaluation of the predictors of choledocholithiasis: comparative analysis of clinical, biochemical, radiological, radionuclear, and intraoperative parameters. Surg Today 2001; 31:117-122
24. Al-Moflech IA, Aljebreen AM, Al-Amri SM, Al-Rashed RS, Al Faleh M, Al-Freihi HM, Abdo AA, Isnani AC: Biochemical and radiological predictors of malignant biliary strictures. World J Gastroenterol 2004; 10:1504-1507
25. Safi F, Schlosser W, Falkenreck S, Beger HG: CA19-9 serum course and prognosis of pancreatic cancer. Int J Pancreatol 1996; 20:155-161
26. Chen CY, Shiesh SC, Tsao HC, Lin XZ: The assessment of biliary CA 125, CA 19-9 and CEA in diagnosing cholangiocarcinoma-the influence of sampling time and hepatolithiasis. Hepato-Gastroenterology 2002; 49:616-620

27. Kim YT, Byun JS, Jang YH: Factors predicting concurrent cholangiocarcinomas associated with hepatolithiasis. Hepato-Gastroenterology 2003; 50:8-12
28. Tangkijvanich P, Thong-ngam D, Theamboonlers A: Diagnostic role of serum interleukin 6 and CA 19-9 in patients with cholangiocarcinoma. Hepato-Gastroenterology 2004; 51:15-19
29. Stain SC, Marsri LS, Froes ET, Sharma V, Parekh D: Laparoscopic cholecystectomy: laboratory predictors of choledocholithiasis. Am Surg 1994; 60:767-771
30. Barone D, Onetto M, Conio M, Paganuzzi M, Saccomanno S, Aste H, Pugliese V: CA19-9 assay in patients with extrahepatic cholestatic jaundice. Int J Biol Markers 1988; 3:95-100
31. Saltztein EC, Peacock JB, Thomas MD: Preoperative bilirubin, alkaline phosphatese and amylase levels as predictors of common bile duct stones. Surg Gynecol Obsestr 1982; 154:381-384
32. Steer ML: Timing of surgery for gallstone pancreatitis. Gastroenterology 1986; 91:780-785
33. Prat F, Amouyal G, Amouyal P: Prospective controlled study of endoscopic ultrasonography and endoscopic retrograde cholangiography in patients with suspected common bile duct stones. Lancet 1996; 347:75-79
34. Canto MIF, Chak A, Stellato T, Sivak MV: Endoscopic ultrasonography versus cholangiography for the diagnosis of choledocholithiasis. Gastrointest Endosc 1998; 47:439-448