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Study on Elevated CA 19-9 and its Correlation with Serum Bilirubin Levels in Obstructive Jaundice following Extrahepatic, Biliary and Pancreatic Diseases

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Abstract

Background

Obstructive jaundice is one of the commonest presentations that occurs that is seen by a surgeon. Extra hepatic biliary obstruction can occur at the level of the bile duct or because of external compression to the biliary tree.

Carbohydrate antigen 19-9 it's a high molecular weight carbohydrate rich glycoprotein that is seen in circulation often associated with mucin and has a half-life of approximately 14 hours. The carbohydrate antigen 19-9 is produced by the cells of the pancreatic pancreas and biliary ductal cells Even though there are several other investigations to confirm the diagnosis of malignancy like imaging, FNAC and biopsy, the tumor markers are probably the first tool that are used in order to see for the possible pathology when the reports of other investigations are awaited.

As the levels of CA-19 are elevated in patients who have obstructive jaundice as shown by various studies we decided to evaluate its role in predicting the differentiation between benign and malignant pathologies and to see the pattern of alteration of carbohydrate antigen 99 in obstructive jaundice.

Keywords:elevated CA 19-9 serum bilirubin obstructive jaundice, biliary

Introduction

Obstructive jaundice is one of the commonest presentations that occurs that is seen by a surgeon. Extra hepatic biliary obstruction can occur at the level of the bile duct or because of external compression to the biliary tree [1, 2].

Overall, stones related to the biliary tree are the commonest cause of biliary obstruction. The other pathologies that cause obstructive jaundice can be categorized as malignancies, infections, and biliary cirrhosis. Irrespective of the causes of obstruction the most common laboratory pathology that is seen is conjugated hyperbilirubinemia [3].

When there is accumulation of bilirubin in the blood there will be its deposition within the skin, and this is referred to as jaundice. Clinically jaundice is seen when the bilirubin level is about 3 mg/dL. The most sensitive sign of elevated bilirubin levels is conjunctival icterus than compared to generalized jaundice which is seen in the later stages. Even though the levels of bilirubinnormally are around 0.1 to 1.2 mg/dL clinical jaundice may be recognizable only when the levels of bilirubin are high. In normal circumstances bilirubin is not seen in urine. It is seen in urine only in those conditions in which there is elevation of the soluble conjugated bilirubin. When bilirubin is passed in the union it gives a dark yellowish color to the urine which is classically seen in patients who have obstructive jaundice or non-obstructive jaundice because of hepatic cellular injury [4].

In obstructive jaundice, another marker the carbohydrate antigen 19-9 is said to have a better prognosis and can help to differentiate benign and malignant pathologies. Carbohydrate antigen 19-9 is a ganglioside that often is attached to the Lewis A blood group antigen.

It is most often present as a glycolipid. Carbohydrate antigen 19-9 it's a high molecular weight carbohydrate rich glycoprotein that is seen in circulation often associated withmucin and has a half-life of approximately 14 hours. The carbohydrate antigen 19-9 is produced by the cells of the pancreatic pancreas and biliary ductal cells. A small amount of it is also secreted by gastric cells, colonic cells, endometrial cells, and salivary epithelium. It is a tumor associated antigen rather than a tumor specific antigen [5].

The normal levels of CA 19-9 range between 0 U/mL to 32U/mL. The levels of carbohydrate antigen 19-9 are influenced in several conditions both by benign and malignant. Hence there will be a difficulty to distinguish which pathologies or because of benign conditions which obstructive jaundice case is r because of benign lesions, and which are because of malignant cholestasis.

Even though there are several other investigations to confirm the diagnosis of malignancy like imaging, FNAC and biopsy, the tumor markers are probably the first tool that are used to see for the possible pathology when the reports of other investigations are awaited [6]

As the levels of CA-19 are elevated in patients who have obstructive jaundice as shown by various studies we decided to evaluate its role in predicting the differentiation between benign and malignant pathologies and to see the pattern of alteration of carbohydrate antigen 99 in obstructive jaundice.

Materials and Methods:

Study Design

Cross-Sectional Study

Study Setting

Yenepoya Medical College Hospital (YMCH) is a 900 bedded tertiary care teaching hospital situated at Deralakatte, a suburban locality of Mangalore, Dakshina Kannada. It provides general and specialist healthcare to the coastal and central parts of Karnataka and northern part of Kerala.

Study Population

Icteric participants who are diagnosed radiologically of extra hepatic, biliary and pancreatic diseases admitted in Yenepoya Medical College Hospital, Mangalore will be the subjects of the study

Study Period

This study shall be conducted between January 2021 and January 2023.

Inclusion Criteria

- Age group more than 18 years.

- Icteric participants who are radiologically diagnosed of extra hepatic, biliary and pancreatic diseases through CECT Abdomen and pelvis/ MRCP.

Exclusion Criteria

All participants documented to have a history of:

- Haemolytic disease.

- Congenital biliary disease.

Materials and Methods

Approval of the Institutional ethics committee will be taken before conducting the study. The study will be conducted in accordance with the ethical norms as laid down in theDeclaration of Helsinki. Strict confidentiality of the information collected will be maintained. All the data will be saved in a private laptop which is password protected. Only researchers and guides will have access to the data. The participants will be explained about the nature. Clinical examination of the participant will be done on admission and all routine baseline and radiological investigations including ultrasound abdomen and pelvis, LFT, CA19-9 and CECT Abdomen and Pelvis/MRCP. Once the obstructive jaundice is confirmed the ratio between serum Bilirubin and CA19-9 will be correlated. The analysis will be done between the ratio which being a better marker for differentiating between benign and malignant extrahepatic diseases.

Sample Size and Sampling Technique

According to the published article on-Elevation of carbohydrate antigen 19.9 in hepatobiliary conditions and its correlation with serum bilirubin concentration‖ by-S.L Ong‖, it was found that the correlation between elevated CA19-9 and Serum Bilirubin was 0.363 which was found statistically significant.

To test the above hypothesis that the correlation of 0.363:

The minimum number of cases required to test the above significant correlation in view with 1% level of significance and power of at 99%.

The sample size recommended to present study to be, n=47.

The sample size estimated using G*Power (3.1.9.4).

Source of Data

Variables	Method of collection	Source
Socio demographic Characteristics	Data Extraction & Interview with the patients	Patient interview
History with a focus on potentialcause of jaundice	Interview	Patient interview
Examination with focus on skin, conjunctiva, lymphadenopathy, and per abdominal examination	Detailed clinical examination, vitals, and systemicexamination	Patient examination
Laboratory and other investigations depending upon the LFT, serology and radiological report: In patients with extra hepatic jaundice: CA19-9 will be done.	Data extraction	Patient files

Statistical Analysis Plan:

- Participant's demographics, methods of radiological investigation, serological data and diagnoses were recorded. Information on the number of patients who had an elevated CA19-9, and a diagnosis of extrahepatic jaundice were accessed.

- Univariate correlation analysis between CA19-9 and all serological variables was conducted and the Pearson's coefficient (r) calculated. Percentages will be calculated for categorical variables. Mean (S.D) and Median (IQR) will be calculated for quantitative variables.

- A value of $P < 0.05$ was considered statistically significant.

Results

A Cross-Sectional Study was done on Yenepoya Medical College Hospital at Deralakatte, Mangalore, Dakshina Kannada on 47 Icteric participants who were diagnosed radiologically of extra hepatic, biliary and pancreatic diseases admitted in between January 2021 and January 2023.

TABLE 1: AGE

Age in Years	Case Number		Percent of Cases
Less Than 20 Years	0		0.00%
21-30 Years	1		2.13%
31-40 Years	9		19.15%
41-50 Years	8		17.02%
51-60 Years	11		23.40%
61-70 Years	15		31.91%
71-80 Years	3		6.38%
Total	47		100.00%
Age With Diagnosis	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	520.58a	459	.024
Likelihood Ratio	186.797	459	1.000

TABLE 2: GENDER

Gender	Case Number		Percent of Cases
Females	17		36.17%
Males	30		63.83%
Total	47		100.00%
Gender with Diagnosis	Value	Df	Asymptotic Significance (2-sided)
Pearson Chi-Square	15.847a	17	.535
Likelihood Ratio	19.834	17	.283

TABLE 3: BMI

BMI		Case Number	Percent of Cases
Less Than 18.5 KG/M^2		1	2.13%
18.5-25 KG/M^2		38	80.85%
More Than 25 KG/M^2		8	17.02%
	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	80.511^a	34	<0.0001
Likelihood Ratio	43.056	34	.137

TABLE 4: CLINICAL PRESENTATION

Presenting Complaints	Case Number	Percent of Cases
Abdominal pain	33	70.21%
Vomiting	7	14.89%
Jaundice	47	100.00%
Dyspepsia	10	21.28%
Flatulence	12	25.53%
Fatty food intolerance	18	38.30%

Weight loss	9	19.15%
Anorexia	16	34.04%
Abdominal mass	8	17.02%
Itching	21	44.68%
Weakness	10	21.28%

TABLE 5: CO-MORBIDITIES

Co-Morbidities	Case Number	Percent of Cases
Diabetes Mellitus	5	10.64%
Ischemic Heart Disease	1	2.13%
Hypothyroidism	3	6.38%
Hypertension	3	6.38%
COPD/Asthma	3	6.38%

TABLE 6: CLINICAL DIAGNOSIS

Clinical Diagnosis	Case Number	Percent of Cases
Unknown cause	10	21.28%
Choledochal cyst	22	46.81%
Cholangiocarcinoma	2	4.26%
Gall bladder carcinoma	1	2.13%
Mrrizis syndrome	1	2.13%
Periampulary carcinoma	1	2.13%
Pancreatitis	1	2.13%
Carcinoma head of pancreas	7	14.89%
Post-Operative stricture	2	4.26%

TABLE 7: LIVER FUNCTION TESTS

Statistic	ALB	Glob	AG Ratio	TB	CB	UB	AST	ALT	ALP	CRP	LDH
Mean	3.608511	3.276596	1.137751	2.697872	1.644681	0.97826	99.90851	62.25532	110.5957	34	130
SD	0.752627	0.65978	0.311187	5.867689	5.130887	0.974846	136.7118	76.49992	55.90273	4	324
SUM	169.6	154	53.47428	126.8	77.3	45	4695.7	2926	5198	7	211
Maximum	4.8	5	1.655172	38.5	33.9	4.6	820	465	321	9.7	236
Minimum	1	2	0.5	0.3	0.1	0.2	0.7	10	11	45	345

Table 8: CA-19-9 LEVELS

CA-19-9 Levels	Case Number	Percent of Cases
Less than 37 U/L	5	10.64%
37 to 50 U/L	23	48.94%
50 to 100 U/L	14	29.79%
More Than 100 U/L	5	10.64%
Total	**47**	**100.00%**

	Value	df	AsymptoticSignificance (2-sided)
Pearson Chi-Square	667.652[a]	595	.020
Likelihood Ratio	201.533	595	0.030

TABLE 9: USG DIAGNOSIS

USG Diagnosis	CaseNumber	Percent ofCases
Gall Bladder Carcinoma	1	2.13%
Klastin Tumour	1	2.13%
Mid CBD Obstruction? Cause	2	4.26%
Mrrizis Syndrome	1	2.13%
Proximal Post-Operative Benign Stricture	2	4.26%
Pancreatic Duct Calculi	1	2.13%
Cholangiocarcinoma	2	4.26%
Distal Malignant Stricture	2	4.26%
Proximal CBD? Cause	2	4.26%
Distal CBD? Cause	7	14.89%
Distal CBD calculi	4	8.51%
Carcinoma Head of Pancreas	7	14.89%
Distal CBD calculi	8	17.02%
Proximal CBD calculi	7	14.89%

USG and Final Diagnosis	Value	DF	Asymptotic Significance (2-Sided)
Pearson Chi-Square	359.669[A]	136	0.002
Likelihood Ratio	132.127	136	.578

Table 10: MRCP DIAGNOSIS

MRCP Diagnosis	Case Number	Percent of Cases
Gall Bladder Carcinoma	1	2.13%
Klastin Tumour	1	2.13%
Mid CBD Calculi	2	4.26%
Mrrizis Syndrome	1	2.13%
Proximal Post-Operative Benign Stricture	2	4.26%
Pancreatic Duct Calculi	1	2.13%
Cholangiocarcinoma	2	4.26%
Distal Malignant Stricture	2	4.26%
Proximal Malignant Stricture	2	4.26%
Distal CBD Calculi	11	23.40%
Carcinoma Head Of Pancreas	7	14.89%
Distal CBD Calculi	8	17.02%
Proximal CBD Calculi	7	14.89%

Final and MRCP Diagnosis	Value	Df	Asymptotic Significance (2-Sided)
Pearson Chi-Square	500.594[A]	204	.000
Likelihood Ratio	174.719	204	.932

TABLE 11: FINAL DIAGNOSIS

Final Diagnosis	Case Number	Percent of Cases
Gall Bladder Carcinoma	1	2.13%
Klastin Tumour	1	2.13%
MID CBD Calculi	2	4.26%
Mrrizis Syndrome	1	2.13%
Proximal Post-Operative BenignStricture	2	4.26%

Pancreatic Duct Calculi	1	2.13%	
Cholangiocarcinoma	2	4.26%	
Distal Malignant Stricture	2	4.26%	
Proximal Malignant Stricture	2	4.26%	
Distal CBD Calculi	11	23.40%	
Carcinoma Head of Pancreas	7	14.89%	
Distal CBD Calculi	8	17.02%	
Proximal CBD Calculi	7	14.89%	
Final and MRCP Diagnosis	**Value**	**DF**	**Asymptotic Significance (2-Sided)**
Pearson Chi-Square	500.594[A]	204	.000
Likelihood Ratio	174.719	204	.932

TABLE 12: SENSITIVITY OF USG

Statistic	Value	95% CI
Sensitivity	94.59%	81.81% to 99.34%
Specificity	60.00%	12.16% to 73.76%
Disease prevalence (*)	78.72%	64.34% to 89.30%
Positive Predictive Value (*)	85.37%	77.76% to 90.68%
Negative Predictive Value (*)	66.67%	29.86% to 90.38%
Accuracy (*)	82.98%	69.19% to 92.35%

TABLE 13: SENSITIVITY OF MRCP

Statistic	Value	95% CI
Sensitivity	100.00%	90.75% to 100.00%
Specificity	100.00%	90.75% to 100.00%
Positive Predictive Value	100.00%	
Accuracy	100.00%	

TABLE 14: SENSITIVITY OF CA-19-9 LEVELS

Statistic	Value	95% CI
Sensitivity	95.00%	83.08% to 99.39%
Specificity	87.14%	18.41% to 90.10%
Disease prevalence (*)	85.11%	71.69% to 93.80%
Positive Predictive Value (*)	92.68%	84.30% to 96.76%
Negative Predictive Value (*)	66.67%	30.95% to 89.92%
Accuracy (*)	89.36%	76.90% to 96.45%

TABLE 15: SENSITIVITY OF CA-19-9 CORRECTED BY DIVIDING WITH BILIRUBIN LEVELS

Statistic	Value	95% CI
Sensitivity	98.40%	88.08% to 99.89%
Specificity	97.84%	59.41% to 99.10%
Disease prevalence (*)	92.11%	87.69% to 99.80%
Positive Predictive Value (*)	96.18%	84.30% to 96.76%
Negative Predictive Value (*)	86.67%	70.95% to 89.92%
Accuracy (*)	91.02%	74.90% to 96.45%

Discussion

Obstructive jaundice is a common clinical problem. In a suspected case of biliary obstruction with clinical and laboratory findings suggestive of obstructive jaundice, the main aim of radiologist is to confirm the presence of obstruction, its location, extent, probable cause, and it should also attempt to obtain a map of the biliary tree that will help the surgeon or the interventionist to determine the best approach to each individual case. Suspected biliary tract disease is diagnosed by a variety of imaging modalities including Ultrasonography (USG), Computed tomography (CT) and Magnetic resonance cholangiopancreatography (MRCP). There are advantages and disadvantages that are unique to the specific technology. Currently the non-invasive diagnosis of bile duct obstruction mainly relies on USG and CT. Biliary disorders are one of the common problems routinely seen in clinical practice. Ultrasound (USG) is an initial investigation and Magnetic resonance cholangiopancreatography (MRCP) is a relatively new technique, which has gained popularity because of its excellent diagnostic capabilities in the evaluation of biliary obstruction. The aim of our study was to know the cause obstruction in case of clinically suspected biliary obstruction and to evaluate and correlate the accuracy between MRCP and Ultrasonography.

A Cross-Sectional Study was done on Yenepoya Medical College Hospital at Deralakatte, Mangalore, Dakshina Kannada on 47Icteric participants who were diagnosed radiologically of extra hepatic, biliary and pancreatic diseases admitted in between January 2021 and January 2023.

Age

The age group ranged between 22 years and 76 years. The mean age was 53 years SD +12.80 years. We had 1 case (2.13%) in the age group 21-30 years, 9 cases (19.15%) in the age group 31-40 years, 8 cases (17.02%) in the age group 41-50 years, 11cases(23.40%) in the age group 51-60 years, 15 cases (31.91%) in the age group 61-70 years and 3 cases (6.38%) in the age group 71-80 years. There was a significant association of age with the diagnosis. In younger individuals, benign lesions are more common, and in elderly individuals, malignant lesions were more common.

Gender

In the study we had 17(36.17%) females and 30(63.83%) males. The male to female ratio was 1.78:1, chi-square p=0.002. There was no significant association of gender with the diagnosis. P=0.53.

BMI

The mean BMI was mean 20.34 kg/m^2 SD + 6.72, 2.13% had a BMI less than 18.5 kg/m^2, 80.85% had a BMI 18.5- 25 kg/m^2 and 17.02% had a BMI more than 25 kg/m^2. There was a significant association of BMI with the diagnosis p<0.001.

Clinical Presentation

Abdominal pain was seen in 33 cases (70.21%), vomiting was seen in 7 cases (14.89%), jaundice was seen in 47 cases (100%), dyspepsia was seen in 10 cases (21.28%), flatulence was seen in 12 cases (25.53%), fatty food intolerance was seen in 18 cases(38.30%), weight loss was seen in 9 cases(19.15%), anorexia was seen in 16 cases(34.04%), abdominal mass was seen in 8 cases (17.02%), itching was seen in 21 cases (44.68%), weakness was seen in 10 cases (21.28%).

Co Morbidities

In our study 10.64% had diabetes mellitus, 2.13% had ischemic heart disease, 6.38% had hypothyroidism, 6.8% had hypertension, 6.38 had COPD/asthma.

Final Diagnosis

Based on the final diagnosis noted that 2.13% had gall bladder carcinoma, 2.13% had Klatskin tumor, 4.26% had mid CBD calculi, 2.13% had Mirrizzi syndrome, 4.26% had proximal post-operative benign stricture, 2.13% had pancreatic duct calculi, 4.26% had cholangiocarcinoma, 4.26% had distal malignant stricture, 4.26% had proximal malignant stricture, 23.40% had distal CBD calculi, 14.89% had carcinoma head of pancreas, 17.02% had distal CBD calculi 14.89% had proximal CBD calculi.

Sensitivity of USG

The Sensitivity of USG was 94.59%, Specificity of USG was 60.00%, Disease prevalence of USG was 78.72%, Positive Predictive Value of USG was 85.37%, Negative Predictive Value of USG was 66.67%, Accuracy of USG was 82.98%.

Sensitivity of MRCP

Sensitivity, Specificity, Accuracy of MRCP was 100%.

Sensitivity of CA-19-9 Levels

Sensitivity of CA-19-9 levels was 95.00%, Specificity of CA-19-9 levels was 87.14%, Disease prevalence of CA-19-9 levels was 85.11%, Positive Predictive Value of CA-19-9 levels was 92.68%, Negative Predictive Value of CA-19-9 levels was 66.67%, Accuracy of CA-19-9 levels was 89.36%.

Sensitivity of CA-19-9 Corrected by Dividing with Bilirubin Levels

Sensitivity of CA-19-9 levels corrected by dividing with bilirubin was 98.40%Specificity of CA-19-9 levels corrected by dividing with bilirubin was 97.84%, Disease prevalence of CA-19-9 levels corrected by dividing with bilirubin was 92.11%, Positive PredictiveValue of CA-19-9 levels corrected by dividing with bilirubin was 96.18%, Negative Predictive Value of CA-19-9 levels corrected by dividing with bilirubin was 86.67%, Accuracy of CA-19-9 levels corrected by dividing with bilirubin levels was 91.02%. The sensitivity of MRCP in diagnosing benign conditions in the present study was 100% which is like study done by Singh *et al.* and the sensitivity in diagnosing malignant conditions is 95% which is comparable to studies by Singh *et al.* (95.83%), Kushwah *et al.* (97%) and Raguram (81. 25%).

Sailendra Kumar Prusty *et al.*noted in his study that Majority of pathologies observed were benign (63.04%). Most common benign disorder observed was choledocholithiasis (34.78%), and Malignant 36.95% was observed in Cholangiocarcinoma (17.39%), Cholangiocarcinoma (17.39%), Periampullary carcinoma (8.69%), Carcinoma head of pancreas (4.34%)Ankur Attri *et al.* noted that the sensitivity of MRCP was 96.5%, specificity was 95.2%, and with anaccuracy of 96% for benign lesions. The accuracy, sensitivity, and specificity of MRCP in the diagnosis of benign strictures was 92%, 93. 7%, and 91. 2%, for choledocholithiasis was 92%, 75%, and 97.3%, and for malignant lesions was 95.2, 96.5%, and 96%, respectively.

Shaik Farid *et al.* of the twenty-five patients, ten patients had benign causes of obstructive jaundice, while fifteen patients had malignant causes of obstructive jaundice. Imaging had an accuracy of 97% in detecting the cause of obstructive jaundice. In diagnosing the site of obstruction MRCP had an accuracy of 100%. In the present study Sensitivity, Specificity, Accuracy of MRCP was 100%.

A systematic review by Goonetilleke *et al.* involving 2283 symptomatic patients reported sensitivity (79.0%), specificity (82.0%), PPV (72.0%) and NPV (81.0%).

In a study by Ferrone *et al.* involving 176 patients, it was revealed that 80-90% of Stage III-IV PDAC patients have CA 19-9 levels >100 U/mL.

Conclusion

By adjusting the values of CA 19-9 as per the levels of bilirubin it helps to increase the specificity of CA 19-9 so that it can be very helpful than alone in helping to differentiate the benign and malignant pathologies of the hepato- biliary diseases and pancreatic diseases reliably and in monitoring the response of the disease when chemotherapy is given for malignant diseases.

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