



Diagnostic accuracy of serum CA 19-9 levels for malignancy in obstructive jaundice using histopathology as the reference standard: a cross-sectional study

Suman Aamir¹, Fatima Rauf¹, Romana Imtiaz¹, Muhammad Rawal Saeed¹, Iffat Noureen¹, Usman Qureshi¹, Muhammad Hanif¹

Correspondence: Fatima Rauf, Benazir Bhutto Hospital, Rawalpindi, Pakistan. Email: fatimarauf005@gmail.com

Abstract

Introduction: Obstructive jaundice is a common presentation caused by benign and malignant hepatobiliary or pancreatic disease. Serum carbohydrate antigen 19-9 (CA 19-9) is frequently raised in malignant obstruction but can also rise with cholestasis and inflammation, which may limit diagnostic specificity. We assessed the diagnostic accuracy of serum CA 19-9 for malignancy in obstructive jaundice using histopathology as the reference standard.

Methods: We conducted a cross-sectional validation study over one year in the Department of General Surgery, Benazir Bhutto Hospital, Rawalpindi, Pakistan. Consecutive patients aged 15 to 65 years with obstructive jaundice, defined biochemically and clinically, were enrolled after consent. Serum CA 19-9 was measured by radioimmunoassay in a single private laboratory. A threshold of ≥ 200 IU/mL defined a positive index test. Endoscopic Retrograde Cholangio Pancreatography with brush cytology provided specimens for histopathology, which served as the reference standard. Sensitivity, specificity, positive predictive value, negative predictive value, and overall diagnostic accuracy were calculated from two-by-two tables with age stratified analyses.

Results: Two hundred and thirty two patients were included. The mean age was 51.9 ± 10.8 years and mean symptom duration was 15.5 ± 7.7 days. There were 144 men (62.07%) and 88 women (37.93%). Using the prespecified threshold, CA 19-9 indicated suspected malignancy in 123 patients (53.02%), while histopathology confirmed malignancy in 95 (40.95%). Overall sensitivity was 87.4%, specificity 70.8%, positive predictive value 67.5%, negative predictive value 89.0%, and diagnostic accuracy 77.6%. In patients aged 15 to 56 years, sensitivity was 93.9% and specificity 56.5%; in those aged 57 to 65 years, sensitivity was 80.4% and specificity 85.3%.

Discussion: Serum CA 19-9 at a threshold of ≥ 200 IU/mL provides supportive evidence for malignancy in obstructive jaundice but lacks sufficient specificity to function as a stand-alone discriminator. Interpretation should be integrated with clinical assessment, biochemistry, imaging, and tissue diagnosis, and consideration given to reassessment after biliary decompression.

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Introduction

Obstructive jaundice is a clinical state in which bile outflow is impeded along the path from the liver to the duodenum¹. It arises from a spectrum of benign and malignant hepatobiliary or pancreatic disorders, and reported proportions of malignancy among affected

patients vary considerably between series²⁻⁴. Accurate discrimination between malignant and benign aetiologies is essential because management strategies and prognoses differ substantially^{5,6}.

Carbohydrate antigen 19-9 is a tumour associated glycan expressed by epithelial cells of the pancreas

¹Benazir Bhutto Hospital, Rawalpindi, Pakistan



and biliary tree and is frequently raised in malignancy related obstruction^{6,7}. The marker is also used for staging assessments, evaluation of resectability, and monitoring for recurrence in pancreatobiliary cancers^{8,9}. However elevations occur in several benign conditions including cholangitis and choledocholithiasis and in non hepatobiliary malignancies which limits diagnostic specificity in patients with jaundice^{10,15,22-24}.

In pancreatic cancer the reported performance of CA 19-9 includes sensitivities around 79% to 81% and specificities around 80% to 82%, although early stage tumours may not produce raised levels^{13,20,21}. The diagnostic characteristics are strongly influenced by the threshold selected, since raising the cut off improves specificity at the expense of sensitivity whereas lowering it has the converse effect^{18,20,21}. Thresholds validated for pancreatic cancer are often applied to biliary tract malignancies but the presence of obstruction and cholestasis can inflate values and confound interpretation^{15,16}.

Case reports and observational studies have documented very high CA 19-9 concentrations in benign biliary disease, including values in the thousands in acute cholangitis or choledocholithiasis, which illustrates the potential for false positive interpretations when the marker is viewed in isolation^{16,17,29}. Accordingly clinicians are advised to interpret CA 19-9 within the context of history, examination, biochemical indices including bilirubin, and imaging or endoscopic findings^{19,25}. The present study evaluates the diagnostic accuracy of serum CA 19-9 for malignancy among patients presenting with obstructive jaundice using histopathology as the reference standard.

Methods

Study design and setting

This cross-sectional validation study was conducted in the Department of General Surgery over a one-year period. A total of 232 patients were enrolled. The sample size was calculated using an expected prevalence of malignancy of 42%, sensitivity of 90.9%, and specificity of 66.7% for serum CA 19-9 in detecting malignant biliary obstruction, with a desired precision of 10%, and a two-sided alpha of 0.05 and 80% power.

Eligibility, recruitment and consent

Inclusion criteria were patients aged 15–65 years of either gender presenting with obstructive jaundice, defined as

serum total bilirubin ≥ 2.5 mg/dl and direct bilirubin > 2 mg/dl with clinically evident jaundice (yellow skin and sclera), of any symptom duration. Exclusion criteria were patients unfit for biopsy and known cases of malignancy. After ethical approval by the CPSP and institutional review board, eligible patients were recruited from the surgical emergency department and written informed consent was obtained from all participants.

Procedures and data collection

Demographic data (age, gender), clinical history, and symptom duration were documented on a pre-designed proforma. Venous blood was drawn from each patient for serum CA 19-9 testing, after which ERCP was performed to relieve obstruction and obtain cytological samples for histopathological analysis.

Index test: serum CA 19-9

Serum CA 19-9 levels were measured via radioimmunoassay at a single private laboratory to ensure consistency. A cut-off value of ≥ 200 IU/ml was considered suggestive of malignancy¹¹.

Reference standard (histopathology)

All patients underwent Endoscopic Retrograde Cholangio-Pancreatography (ERCP) with brush cytology. Specimens were submitted to the hospital's histopathology department, where a consultant histopathologist provided the definitive diagnosis.

Outcome measures

Diagnostic performance of serum CA 19-9 was assessed using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy, with histopathology as the gold standard. Definitions were: true positive (TP), CA 19-9 ≥ 200 IU/ml and malignancy on histopathology; true negative (TN), CA 19-9 < 200 IU/ml and no malignancy on histopathology; false positive (FP), CA 19-9 ≥ 200 IU/ml with no malignancy on histopathology; and false negative (FN), CA 19-9 < 200 IU/ml despite malignancy on histopathology.

Data analysis

Data were analysed using SPSS version 23. Quantitative variables (e.g., age, duration of symptoms) were reported as means \pm standard deviation, and



qualitative variables (e.g., gender, malignancy status) as frequencies and percentages. Sensitivity, specificity, PPV, NPV, and accuracy were calculated using 2x2 contingency tables with histopathology as the reference standard. Stratification was performed for age, with post-stratification diagnostic values calculated.

Ethics

The study was conducted after approval from the ethical review board, and informed consent was obtained from all participants.

Table 1: Comparison of malignancy on histopathology to suspected malignancy on serum CA 19-9 Levels

Malignancy on histopathology	Suspected malignancy on serum CA 19-9 levels	
	Yes	No
Yes	83	12
No	40	97

Sensitivity: 87.4%, specificity: 70.8%, PPV: 67.5%, NPV:89%, diagnostic accuracy: 77.6%

Results

Two hundred and thirty two patients met the inclusion criteria and were enrolled. The mean age was 51.9 years with a standard deviation of 10.8 and ranged from 15 to 65 years. The mean duration of symptoms was 15.5 days with a standard deviation of 7.7 and ranged from 4 to 30 days. There were 144 men which was 62.07% and 88 women which was 37.93%.

Using a prespecified threshold of at least 200 IU per mL for CA 19-9, suspected malignancy was indicated in 123 patients which was 53.02% whereas 109 patients which was 46.98% did not meet the threshold. Histopathology confirmed malignancy in 95 patients which was 40.95% and benign disease in 137 patients which was 59.05%. The corresponding diagnostic performance metrics were sensitivity 87.4%, specificity 70.8%, positive predictive value 67.5%, negative predictive value 89.0%, and overall diagnostic accuracy 77.6%.

Age stratified analyses showed that in patients aged 15 to 56 years sensitivity was 93.9%, specificity 56.5%, positive predictive value 60.5%, and negative predictive value 92.9%. In patients aged 57 to 65 years sensitivity was 80.4%, specificity 85.3%, positive predictive value 78.7%, and negative predictive value 86.6%. The distribution of CA 19-9 values below 200 and at least 200 IU per mL

by sex and age groups and by final histopathological diagnosis is presented in the study tables.

Table 2: Stratification of age to determine the association of age with malignancy on histopathology to suspected malignancy on serum CA 19-9 Levels. Age group: 15-56 years.

Malignancy on histopathology	Suspected malignancy on serum CA 19-9 levels	
	Yes	No
Yes	46	3
No	30	39

Sensitivity: 93.9%, specificity: 56.5%, PPV: 60.5%, NPV: 92.9%

Discussion

This study evaluated the diagnostic accuracy of serum CA 19-9 for malignancy among patients presenting with obstructive jaundice in a surgical setting using histopathology as the reference standard. Sensitivity was 87.4% and specificity was 70.8% at a threshold of at least 200 IU per mL, with positive and negative predictive values of 67.5% and 89.0% respectively and an overall diagnostic accuracy of 77.6%. These values indicate that CA 19-9 offers supportive evidence but lacks sufficient specificity to serve as a solitary discriminator between malignant and benign causes of obstruction.

Our findings align with reports that CA 19-9 performance depends on context and threshold, and that cholestasis and inflammation can produce false positive elevations^{16,18,20,21,25}. Benign hepatobiliary and gastrointestinal conditions including cholecystitis, cholangitis, choledocholithiasis, primary biliary cirrhosis, pancreatitis, and viral hepatitis have all been associated with raised values, and increases have been noted in non hepatobiliary malignancies²²⁻²⁴. This overlap reduces specificity and underscores the need to interpret the marker alongside clinical and imaging findings¹⁹.

Comparative studies using similar thresholds provide useful context. Bhuyian and colleagues reported sensitivity 90.9% and specificity 66.7% at 200 IU per mL and our estimates are close to these values¹¹. Anwar and colleagues explored a ratio of CA 19-9 to C reactive protein as an adjunct to improve discrimination which reflects ongoing attempts to mitigate false positives from inflammatory states¹².

Threshold selection is a central determinant of test characteristics. Morris Stiff and colleagues used a 50



IU per mL threshold with higher sensitivity and lower specificity and observed that combining CA 19-9 with imaging markedly improved diagnostic performance, which supports an integrated diagnostic pathway²⁶. Duffy and colleagues documented that very high thresholds such as 1000 IU per mL yield excellent specificity with substantial losses in sensitivity, whereas conventional thresholds give more balanced but still imperfect performance²⁰. Marrelli and colleagues showed similar shifts in sensitivity and specificity across cut offs and emphasised the effect of biliary obstruction on measured values¹⁶.

Table 3: Stratification of age to determine the association of age with malignancy on histopathology to suspected malignancy on serum CA 19-9 Levels. Age group: 57-65 years.

Malignancy on histopathology	Suspected malignancy on serum CA 19-9 levels	
	Yes	No
Yes	37	9
No	10	58

Sensitivity: 80.4%, specificity: 85.3%, PPV: 78.7%, NPV: 86.6%

Dynamic changes in CA 19-9 after relief of obstruction provide additional discriminatory information. In benign disease substantial falls are often seen after drainage, whereas in malignant disease values may remain elevated or decline only modestly, although overlap persists^{16,26,28}. Case reports describe extreme CA 19-9 elevations in benign cholangitis or choledocholithiasis that normalised following treatment which cautions against over interpreting isolated high results²⁹.

The age stratified results in this study showed higher sensitivity and lower specificity in the younger group and the converse pattern in the older group. These differences may reflect spectrum effects or chance variation and should be interpreted cautiously in the absence of an a priori hypothesis.

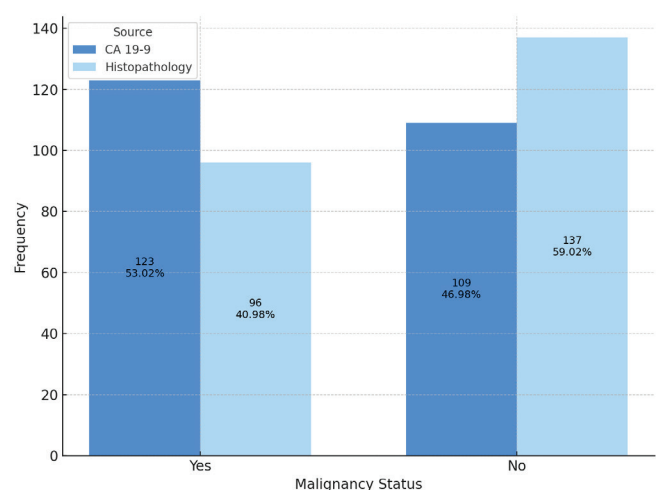
Strengths of the study include the prospective capture of clinical variables, the use of a prespecified index test threshold, and the application of a uniform analytical method at a single laboratory. Limitations include the cross-sectional design which provides a single time point

estimate without evaluating post drainage dynamics, and the use of brush cytology as the reference standard which may misclassify some malignant cases as benign and thus bias estimates of accuracy. We did not compute adjusted thresholds by bilirubin or develop multivariable models that combine clinical and biochemical factors, and these approaches may further refine discrimination in future work^{19,25}.

Table 4: Distribution of patients by serum CA 19-9 levels (<200 vs ≥200 IU/mL) across clinical and demographic groups

Variable	CA 19-9 <200 IU/mL	CA 19-9 ≥200 IU/mL	Total
Gender			
Males	63	81	144
Females	46	42	88
Age Groups			
15–56 years	42	76	118
57–65 years	67	47	114
Diagnosis			
Benign disease	97	40	137
Malignant disease	12	83	95
Total	109	123	232

Figure 1: Comparison of Malignancy Detection by CA 19-9 Levels and Histopathology



Note: Data represents the distribution of malignancy status (Yes/No) based on CA 19-9 tumour marker levels and histopathological findings. Percentages reflect proportion of total cases (n=232) for each method.



In clinical practice the present findings support the use of CA 19-9 as a corroborative marker when malignancy is suspected, interpreted alongside history, examination, bilirubin and other liver indices, and imaging or endoscopic findings. Where diagnostic uncertainty persists tissue diagnosis remains essential, and repeat measurement after biliary decompression may help to distinguish inflammatory from malignant sources of elevation^{16,26,28}.

Serum CA 19-9 measured at a threshold of at least 200 IU per mL provides supportive evidence for malignancy among patients with obstructive jaundice but does not offer sufficient specificity to replace imaging and histopathology. Clinical interpretation should consider the influence of cholestasis and inflammation and should integrate biomarker results with radiological and endoscopic findings.

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