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Original Research Article

A Retrospective Study Showing the Value of the Triple Tumor Markers CA19-9, CA125, and CEA in Predicting the Advanced Stage of Carcinoma Gallbladder

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Abstract

Introduction: The assessment and prognosis of carcinoma gallbladder are determined using a combination of serum tumor markers (GBC). The purpose of the study was to determine the significance of using CA19-9, CA125, and CEA together in metastatic GBC and to determine the cut-off values for each of these tumor markers.

Method: This research involved 40 cases of advanced GBC and was done retrospectively over the course of a year. Based on the results of the CECT scan, the patients were divided into groups for locally progressed and metastatic stages. All patients had their CA19-9, CA125, and CEA levels evaluated. These two groups of GBCs were used to analyze these tumor markers. R statistical software version 3.6.2 was used to conduct the statistical analysis.

Results: Out of 40 instances, 17 (77%), 15 (71%) and 8 (38%) patients with metastatic illness had increased CA19-9, CA125, and CEA levels. The ROC curve was used to calculate the cut-off values for CA19-9, CA125, and CEA, which were >108 U/ml, 55.3 U/ml, and 2.55 µg/l, respectively. For the diagnosis of the metastatic stage of the cancer, CA19-9 exhibited the best sensitivity (78.2%), followed by CA125 (69.5%), and CEA (68.3%). Combining these tumour markers increased their specificity to the greatest extent.

Conclusion: However, their cut-off level is statistically insignificant in predicting metastatic GBC. The combined use of triple tumor markers boosts its specificity in the diagnosis of advanced stages of GBC.

Keywords: Cut-off values for CA19-9, CA125, and CEA in metastatic carcinoma gallbladder, and tumor markers in gallbladder cancer-specific cancer tumor markers in the gallbladder.

Introduction

The most prevalent biliary malignancy is carcinoma of the gallbladder (GBC) [1]. Northern India has a relatively high incidence of it. The tumour is exceedingly aggressive [2]. Due to early, non-specific symptoms, the diagnosis of GBC often delayed. Carcinoembryonic antigen (CEA)

and carbohydrate antigen (19-9) are two common serum tumour indicators in GBC. In advanced GBC, several tumour markers were increased. One Indian study [3] shown the use of CA125 as a tumour marker for GBC. High molecular weight glycoprotein known as CA 125 is a distinguishing antigen connected to coelomic epithelium.

It is produced by the epithelial cells of ovarian carcinomas as well as breast, pleura, and peritoneal lining tumors [4,5]. CA125 has a 4-5 day half-life [6]. In most cases, CA19-9 and CEA are combined. The use of tumour markers as a prognostic or predictive factor.

While predictive factors are linked to the likelihood of sensitivity or resistance to a particular therapy, prognostic factors are used to estimate the risk of illness outcome in the absence of treatment or to estimate the residual risk following treatment [7].

The study's objectives were to determine the importance of using the triple tumour markers CA19-9, CA125, and CEA in combination in advanced stages of GBC and to determine the cut-off value for each of these tumor markers in predicting the metastatic stage of GBC.

Methods

Retrospective observational cohort analysis on cases of advanced GBC admitted to a single unit of Department of Surgery in Jawaharlal Nehru Medical College and Hospital from January 2020 to December 2021. The study was retrospective, thus ethical approval wasn't necessary. The patient's identity is kept a secret, though. All adults over the age of 18 who had been given the definitive diagnosis of gallbladder cancer underwent contrast-enhanced computed tomography (CECT) scans of the abdomen and chest, as well as the triple tumour markers CA19-9, CA125, and CEA. Early GBC cases were not included in the study. This observational study followed STROBE principles. Age, gender, serum CA19-9 and CA125 levels, and CEA and CECT scan results were the data that were gathered.

A total of 40 patients were included in the study after meeting the inclusion criteria. Based on the results of the CECT scan, cases were categorized into those with locally advanced (LA) and metastatic (M) disease. All GBC patients were assessed using the triple tumor markers CA19-9, CA125, and CEA, and the tumors' LA and M stages were analyzed. These tumor markers' upper normal reference values were CEA >4 g/l, CA125 34 u/ml, and CA19-9 38 u/ml.

Statistical Analysis

R statistics software version 3.6.2 was used to conduct the statistical analysis. The Wilcoxon-Mann-Whitney U Test was the non-parametric analysis used to compare the data. Fisher's exact test was used to determine the p value because the sample size was tiny, and the t-test was used to compare the means. To determine the correlation between triple tumour markers and the LA and M stages of GBC, the Chi-square test was used. The receiver operating characteristic curve (ROC) was built to determine the test's cut-off value and the importance of the test for diagnosis.

Results

18 (44%) of the 40 cases had LA disease, while 22 (54%) had M illness. 32 female instances and 8 male cases. At the presentation, the average age was 52. In contrast to CA19-9, which was normal in 10 (25%) and high in 30, CA125, which was normal in 11 (32%) and elevated in 29, and CEA, which was normal in 26 (63%) and elevated in 14, GBC was normal in 14 (35%) instances (Table 1).

Table 1: A description of each GBC parameter (n = 40)

Parameter	Mean ± SD	Median (IQR)	(Min-Max)
Age	52.70±12.78	52.51(15.01)	(22.01-84.01)
Gender			
Male	8 (21.3)		
Female	32 (78.5)		
CA-19-9 (U/ml)	1789.55 ± 8824.65	220.24(695.01)	(2.01-5750.01)
CA-19-9 N (%)			
WNL	10 (26.1)		
Raised	30 (73.7)		
CA 125 (U/ml)	422.27 ± 1186.27	59.41 (221.51)	(9.71-6900.01)
CA 125 N (%)			
WNL	11 (33.2)		
Raised	29 (66.6)		
CEA (µg/l)	72.94 ± 250.65	7.63 (12.81)	(0.01-1500.01)
CEA N (%)			
WNL	26 (64.2)		
Raised	14 (35.6)		
Tumor Stage			
Locally advanced	18 (45.1)		
Metastatic	22 (54.7)		

The triple tumour marker was raised in 77% (17), 71% (15), and 38% (8) of patients with metastatic disease when compared to the GBC stage. Despite the fact that none of the tumour indicators were statistically substantially ($p<0.04$) related with the GBC stage.

In order to determine the cutoff value of the triple tumour markers in predicting the M stage of the disease and its diagnostic importance, the receiver operating characteristic curve (ROC) was created. With a sensitivity of 77% and a specificity of 47.3%, metastatic disease is predicted at a cut-off value of CA19-9 >1077 U/ml.

The CA 19-9 (U/ml) area under the ROC curve (AUROC) for predicting M vs LA was 0.562 (95% CI: 0.381-0.743), indicating subpar diagnostic ability. The statistical significance was zero (p=0.494). When CA19-9 (U/ml) is less than 108, the chances ratio (95% CI) for metastatic tumour was 2.54. (0.6-9.30). When CA19-9 (U/ml) is less than 108, the relative risk (95% CI) for metastatic tumour was 1.56. (0.85-3.31).

Again exhibiting poor diagnostic accuracy, the AUROC for CA125 (U/ml) in predicting M vs LA tumour was 0.573 (95% CI: 0.396-0.751). The statistical significance was zero (p=0.418). It predicts metastatic tumour with a sensitivity of 64% and a specificity of 57% at a cut-off of CA125 (U/ml) >55.3. When CA125 (U/ml) is 55.3, the chances ratio (95% CI) for metastatic disease was 2.13. (0.61- 7.36). When CA125 (U/ml) is >55.3, the relative risk (95% CI) for metastatic illness was 1.40. (0.80-2.61).

It can be seen that the diagnostic performance was subpar because the AUROC for CEA (g/l) predicting M vs LA illness was 0.502 (95% CI: 0.323-0.682). Statistically speaking, it was not significant (p=0.981). With a sensitivity of 35% and a specificity of 78%, it predicts metastatic illness at a cut off of CEA (g/l) 2.55. When CEA (g/l) is less than 2.55, the relative risk (95% CI) for metastatic disease is 1.22, and the odds ratio (95% CI) for metastatic disease was 1.63 (0.3-6.75).

Due to the test's lack of statistical significance, all of these cut-off and diagnostic criteria are unreliable. The findings indicate that metastatic GBC has CA19-9 and CA125 levels that are more consistently increased than CEA. The PPV and NPV of triple tumour markers were further examined. Comparatively, CA19-9 and CA125 had sensitivity and specificity of around 77% and 31%, respectively, compared to CEA's sensitivity and specificity of about 38% and 67%, respectively.

Discussion

A molecular or tissue-based process called a tumour marker provides information regarding the potential course of a malignancy. These markers are a result of alterations in malignant tissue or the characteristics of the malignancy that set it apart from other malignancies. Some tumour indicators are found in the circulation, whereas others are found in the tissue where the cancer first developed, local lymph nodes, distant metastatic organs, or regional lymph nodes. It is uncommon to employ tumour markers to determine the tissue of origin of malignancy because they are frequently non-specific to the tissue of origin [7]. The most frequently utilised serum tumour markers for the diagnosis and prognosis of the GBC are CA19-9 and CEA. They work better together to forecast the prognosis than they do separately [8,9].

Unlike CEA, which is a protein polysaccharide complex, CA19-9 is a mucous protein. While CEA is raised in gastrointestinal cancer, pancreatic and biliary tract tumours, and embryonic gut, CA19-9 is elevated in pancreatic, stomach, and bile duct neoplasms [10,11]. Patients with colorectal cancer were the first to receive serum CEA, and patients with ovarian cancer received serum CA125 [7] Even though CA19-9 and CEA are frequently combined as prognostic indicators for pancreatic and stomach cancer, CEA's sensitivity and specificity for biliary tract cancer are subpar [11]. Sensitivity of CA19-9 and CA125 progressively rose as the disease's stage advanced [12].

The current study's findings were in line with those of the earlier study, which demonstrated greater sensitivity of CA19-9 and CA125 in metastatic illness. According to the prior study [13], the sensitivity and specificity of CEA in GBC were subpar, coming in at roughly 39% and 68%, respectively. For the diagnosis and prognosis of advanced GBC, CA19-9 showed the highest sensitivity (78.2%), followed by CA125 (69.5%), and CEA (68.3%), which is comparable with the results of the prior study [12].

The cut-off values for CA19-9, CA125, and CEA in the current investigation were >108 U/ml, 55.3 U/ml, and 2.55 g/l, respectively, as determined by the ROC curve. Contrary to the current study, a study by Shukla's cut values for CA19- 9 and CA125 in GBC were 211.27 U/ml and 253.6 U/ml, respectively [14]. The specificity and diagnostic accuracy for metastatic disease in the current study were 47.3%, 57.8%, 78.8%, and 64.2%, 61.8%, and 54.7% respectively when the value of CA19-9, CA125, and CEA was greater than the cut-off level. This suggests that the combined use of these tumour markers increases its specificity in the diagnosis of advanced GBC. [15]

Conclusion

In this research, the combined use of the triple tumor markers CA19-9, CA125, and CEA was recognized as an independent predictor of the advanced GBC stage. None of these tumour markers' cut-off values, though, are statistically significant in identifying GBC with metastatic disease. CA19-9 and CA125 were more frequently used as GBC advanced-stage predictors than CEA.

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