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Macrophage Inhibitory Cytokine 1 (MIC-1) Versus Carbohydrate Antigen 19–9 (CA 19.9): Diagnostic Efficacy In Pancreatic Ductal Adenocarcinoma

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Abstract:
Background: *CA 19.9 is the most common and validated diagnostic tumor marker for PDAC used in clinical practice. However, it has poor predictive value in patient with no symptoms. Thus, to increase its diagnostic accuracy and avoid dismal prognosis it should be used in combination with other biomarkers. There are some studies on use of MIC-1 in PDAC. But, diagnostic value of MIC-1 particularly in combination with CA19–9 in PDAC is still worth exploring. Thus, this study is planned to find diagnostic efficacy of MIC-1 and CA19.9 in PDAC.*
Methods: *The study includes 35 clinically diagnosed and confirmed cases of PDAC. 35 age and sex matched healthy volunteers were selected and used for comparison of result. The analysis of CA19.9 and MIC-1 was carried out on fully automated chemiluminescent immune analyzer and ELISA reader respectively. ROC analysis of CA-19 and MIC-1 was the major statistical analysis to find cut-off, sensitivity, specificity and diagnostic efficacy of MIC-1 and CA19.9 in PDAC. The results were used to know whether MIC-1 in combination with CA19.9 helps in early detection of PDAC and helps to reduce dismal prognosis.*
Results: *In this study, we found CA 19.9 is more sensitive than MIC-1 (Sensitivity 91.43 % vs 81.25 %). While MIC-1 is more specific than CA 19.9 (Specificity 91.43 % vs 88.57 %). After comparing diagnostic efficacy of CA 19.9 (AUC = 0.971, accuracy = 90 %) and MIC-1(AUC = 0.958, accuracy = 86.57 %), it is found that both CA 19.9 and MIC-1 have nearly equal diagnostic accuracy. Sensitivity and specificity together provide a holistic picture of a diagnostic test. For a test to be novel marker, it should be highly sensitive as well as highly specific. Now, CA 19.9 is more sensitive while MIC-1 is more specific. Thus, combination of CA 19.9 and MIC-1 may increase diagnostic efficacy in pancreatic ductal adenocarcinoma.*
Conclusions: *MIC-1 even being less sensitive, have high specificity and nearly equal accuracy to that of CA 19.9 and hence in combination with CA 19.9, it may increase diagnostic efficacy in PDAC.*
Keywords: *Macrophage Inhibitory Cytokine 1, Carbohydrate Antigen 19–9, Pancreatic Ductal Adenocarcinoma*

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I. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal solid malignancies. Currently, it is the fourth leading cause of cancer death and has the lowest survival rate for any solid cancer.[1] As per Globocan India 2022; 1413316 new cases of cancer were detected including 691178 males and 722138 females in 1.41 billion peoples. In case of pancreatic ductal adenocarcinoma, the number of new cases as per same Globocan were 13661 accounting 0.97 % of total cancer cases. The prevalence for PDAC is 0.49 per 100000 indicating its lethal form.[2,3,4] The most important reason behind poor survival is that most of the patients with PDAC are diagnosed at an advanced stage due to the lack of obvious symptoms, and their prognosis remains very dismal. Only 10% to 15% of patients arrives with small, resectable cancers. Due to late diagnosis and dismal prognosis, currently, it has only 6% 5-year survival rate. Now, as patients with resectable cancers can achieve a 5-year survival of 15% to 40% after pancreatico-duodenectomy, an improved pancreatic cancer diagnosis could save

lives. Indeed, screening individuals whose family history indicates an increased risk of developing pancreatic cancer can lead to the early diagnosis and treatment of their pancreatic neoplasms.[5]

To increase the proportion of cure and/or 5-year survival of PDAC, there is an urgent need to develop an effective screening system for asymptomatic individuals that increases diagnostic accuracy for PDAC in its early stage. Serum is the most ideal biological specimen for assessing tumor markers in clinical practice because of its availability for repeated collection and reproducible quantification. Recent advancements in technology and an increasing understanding of molecular biology have facilitated research programs into serum markers for PDAC.[6]

Currently, serum carbohydrate antigen 19-9 (CA 19.9) is the most common and validated diagnostic tumor marker for PDAC used in clinical practice. However, it has poor predictive value in patient with no symptoms. On other hand, CA 19-9 can be elevated in acute cholangitis, pancreatitis, obstructive jaundice and liver cirrhosis. Additionally, Lewis-negative blood type patient do not produce CA 19-9 levels, thus contributing to false negativity. Thus, to increase its diagnostic accuracy and avoid dismal prognosis it is need to use it in combination with other biomarkers.[7,8]

Macrophage inhibitory cytokine 1 (MIC-1) is weakly and stably expressed in most tissues under normal conditions. But it plays a significant role in carcinogenesis related activities, such as proliferation, migration, apoptosis, and angiogenesis, in many types of solid tumors including PDAC.[9,10]

A previous study identified MIC-1 as a potential novel biomarker for detection of PDAC. A study conducted by Xiaobing Wang et.al. concluded that the combination of MIC-1 and CA19.9 could improve the diagnostic performance of PDAC significantly. Serum MIC-1 is significantly elevated in most PDAC, including those with negative CA19.9 and early-stage disease and thus may serve as a novel marker for detection of pancreatic cancer.[11] A study conducted by Ying Yang et.al. in their meta-analysis found that MIC-1 is a comparable biomarker to CA19–9 as an individual diagnostic tool for pancreatic cancers and each performs its own functions.[12]

Robert Sean O'Neill et.al. in their pilot study reported that. MIC-1/GDF15 has predictive capacity for neoplastic tumors in asymptomatic individuals with pancreatic cancers.[13]

Koopmann et al in their study reported that MIC-1 was differentially expressed in pancreatic cancer tissues and elevated in the serum of pancreatic cancer patients compared with both healthy controls and those with benign pancreatic neoplasms. They also concluded that MIC-1 has only modest ability to distinguish between pancreatic cancer and pancreatitis. Additional studies are needed to determine whether the diagnostic utility of MIC-1 could be improved further by combining MIC-1 not only with CA19–9 but also with other serum markers.[14]

There are only few studies on diagnostic value of MIC-1 in PDAC. Further, diagnostic value of MIC-1 combined with CA19–9 in diagnosis of PDAC is still worth exploring. Thus, this study is planned to find diagnostic efficacy of MIC-1 and CA19.9 in PDAC in order to know whether MIC-1 in combination with CA19.9 helps in early detection of PDAC and helps to reduce dismal prognosis.

II. Material And Methods

The present study was conducted at Government Medical College and Cancer Hospital, Chhatrapati Sambhajinagar during January 2024 to December 2024. The study population included 35 clinically diagnosed and confirmed cases of pancreatic ductal adenocarcinoma (PDAC). 35 age and sex matched healthy volunteers between age 18 to 60 were selected and used for comparison of result. The blood samples of PDAC patients admitted in ICU or Wards at Government Medical College and Cancer Hospital, Chhatrapati Sambhajinagar were collected after diagnosis but before surgical resection. The estimation of carbohydrate antigen 19.9 and MIC-1was carried out on fully automated chemiluminescent immune analyzer and ELISA reader respectively.

Estimation of CA 19.9: Estimation of CA19.9 was carried out on fully automated chemiluminescent immune analyzer working on principle of two site sandwich chemiluminescent immunoassay (CLIA). In first step, test sample, paramagnetic micro-particles coated with monoclonal anti-CA 19.9 antibody and monoclonal anti-CA 19.9 antibody-alkaline phosphate conjugate were added into a reaction cuvette. After incubation, CA 19.9 present in the test sample binds to both anti-CA 19.9 antibody coated micro-particles and anti-CA 19.9 antibody-alkaline phosphate conjugate to form a sandwich complex. Micro-particle was magnetically captured while other unbound substances were removed by washing. In second step, the substrate solution was added to reaction cuvette. The substrate was catalyzed by anti-CA 19.9 antibody-alkaline phosphatase conjugate in the immune-complex retained on the micro-particle. The resulting chemiluminescent reaction was measured as relative light units (RLUs) by the photomultiplier built into the system. The amount of CA 19.9 present in the test sample was proportional to relative light units (RLUs) generated during the reaction. The CA 19.9 concentration determined via a calibration curve and produced automatically by the instrument.

Estimation of MIC-1 : Estimation of MIC-1 was carried out on enzyme linked immune sorbent assay analyzer (ELISA reader). Firstly, microwells were pre-coated with monoclonal antibodies (Anti MIC-1 antibodies). Then, samples and standards were pipetted into the microwells. The analyte (MIC-1) present in the standard and sample bound by the monoclonal antibodies pre-coated in microwells. After that, biotin labeled antibody and Streptavidin: HRP were added into microwells and incubated to form a complex. Washing of microwells was carried to remove any unbound antibodies and TMB substrate solution was added to microwells. The color developed was directly proportionally to the concentration of analyte (MIC-1) present in the sample. Color development was stopped by addition of stop solution and absorbance measured at 450 nm.

Inclusion criteria: Patients with age between 18 to 60, both sex, tobacco addicts, tobacco non-addicts, alcoholics but diagnosed with pancreatic ductal adenocarcinoma were included in the study.

Exclusion criteria: Patients with age < 18 and > 60, patients with any other type of cancer and other pancreatic conditions such as acute and chronic pancreatitis were excluded from the study group.

Statistical analysis: In this study, receiver operating characteristic (ROC) analysis of CA-19 and MIC-1 was the major statistical analysis to find diagnostic efficacy of MIC-1 and CA19.9 in PDAC in order to know whether MIC-1 in combination with CA19.9 helps in early detection of PDAC and helps to reduce dismal prognosis. The area under curve (AUC) was calculated for each marker using ROC curve.

III. Result

The mean, median and standard deviation of both markers CA19.9 and MIC-1 are provided in table 1. In table 2, diagnostic performances of each marker are mentioned.

Cases	CA 19.9 (U/ml)			MIC-1 (pg/ml)		
	Mean	Median	SD	Mean	Median	SD
PDAC (n=35)	646.69	163.38	1064.44	1963.87	1213.0	2049.2
Control (n=35)	19.84	21.44	9.39	295.85	247.5	169.58

Table 1. Serum levels of biomarkers in normal controls and pancreatic cancer

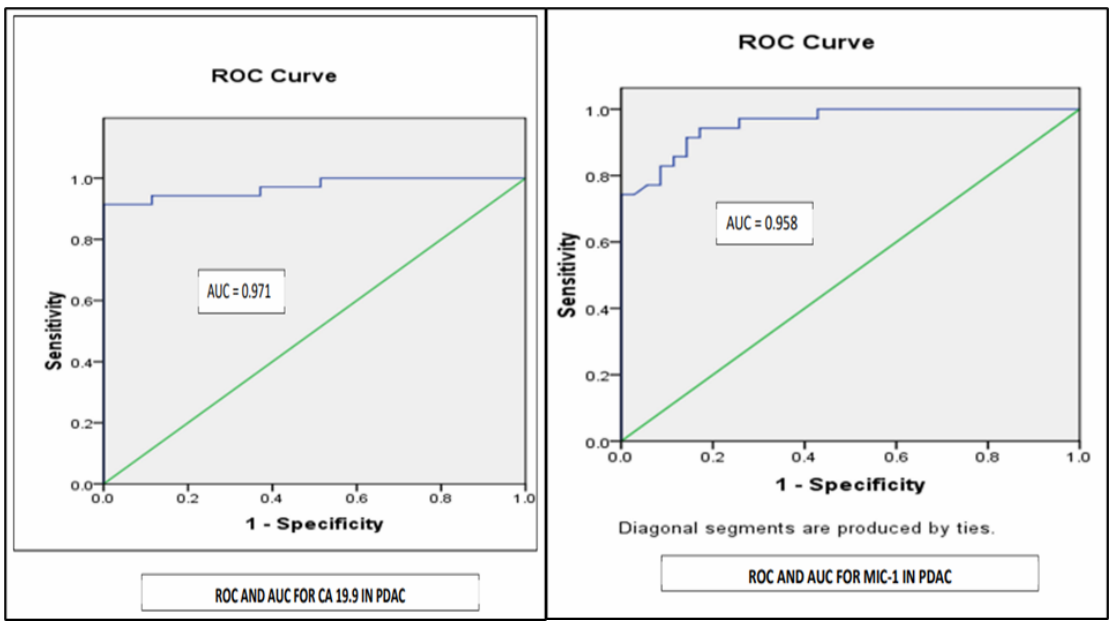

Fig 1 : ROC and AUC for CA 19.9 and MIC-1 in PDAC

Marker	Sensitivity	Specificity	Accuracy	AUC	Positive Predictive Value	Negative Predictive Value
CA 19.9	91.43 %	88.57 %	90.00 %	0.971	88.89 %	91.18%
MIC-1	81.25 %	91.43 %	86.57 %	0.958	89.66 %	84.21 %

Table 2. Diagnostic performance of individual serum markers

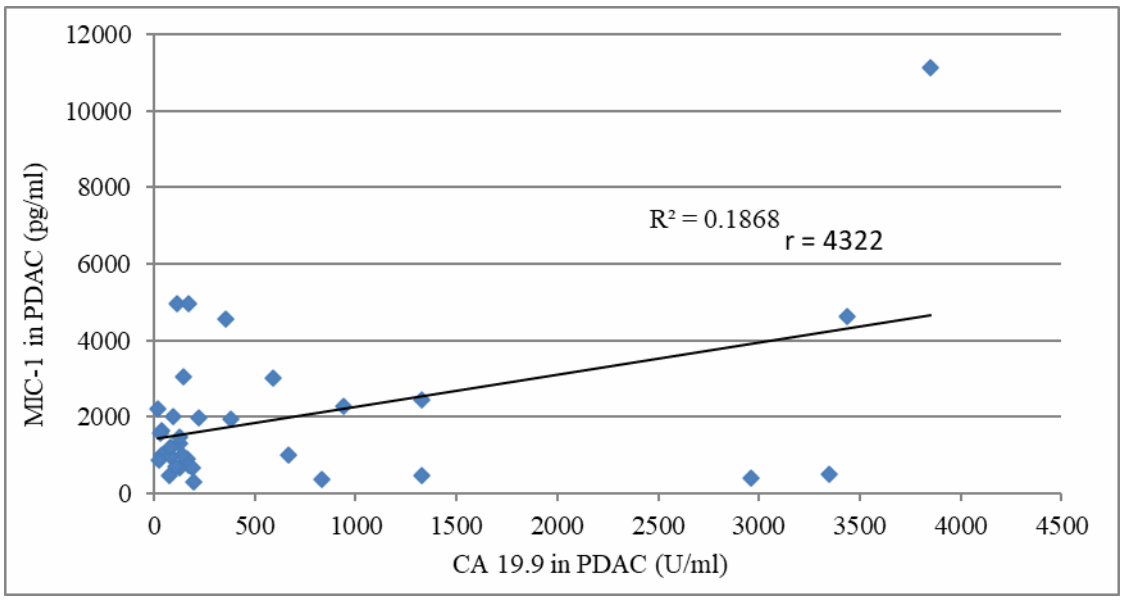

Fig 2 : Co-relation between CA 19.9 and MIC-1 in PDAC

Expression of CA 19.9 and MIC-1 in PDAC

In our study, we estimated levels of CA 19.9 and MIC-1 in both PDAC patients and healthy controls. We found that with compared to normal CA 19.9 (19.84 ± 9.39 U/ml), level of CA 19.9 (646.69 ± 1064.44 U/ml) get significantly ($p<0.01$, $r=0.6319$) elevated in PDAC patients. (Table-1, Figure-2)

On other hand, with compared to normal MIC-1 (295.85 ± 169.58 pg/ml), level of MIC-1 (1963.87 ± 2049.2 pg/ml) also get significantly ($p<0.01$, $r=0.6319$) elevated in PDAC patients. (Table-1, Figure-2)

Diagnostic efficacy of CA 19.9 and MIC-1 in PDAC

Now, to find diagnostic efficacy of MIC-1 and CA19.9, receiver operator characteristic (ROC) curves for CA 19.9 and MIC-1 for PDAC versus healthy controls are obtained by plotting sensitivity versus 1-specificity. To measure diagnostic performance of CA 19.9, we used a cut-off of 30.4 U/ml. At this cut-off, area under curve (AUC) found 0.971 (Asymptotic 95 % CI, 0.0-1.00) (Figure-1).

With this cut-off, sensitivity of CA 19.9 we found from study is 91.43 % (95 % CI, 76.94% to 98.20%) while specificity we found is 88.57 % (95 % CI, 73.26% to 96.80%). The positive predictive value stands 88.89 % (95 % CI, 75.98% to 95.29%) while negative predictive value stands 91.28 % (95 % CI, 77.68% to 96.84%). (Table-2)

On other hand, to measure diagnostic performance of MIC-1, we used a cut-off of 613.94 pg/ml. At this cut-off, area under curve (AUC) found 0.958 (Asymptotic 95 % CI, 0.918-0.998) (Figure-1). With this cut-off, sensitivity of MIC-1 we found from study is 81.25 % (95 % CI, 63.56% to 92.79%) while specificity we found is 91.43 % (95 % CI, 76.94% to 98.20%). The positive predictive value stands 89.66 % (95 % CI, 74.36% to 96.28%) while negative predictive value stands 84.21 % (95 % CI, 72.02% to 91.70%). (Table-2)

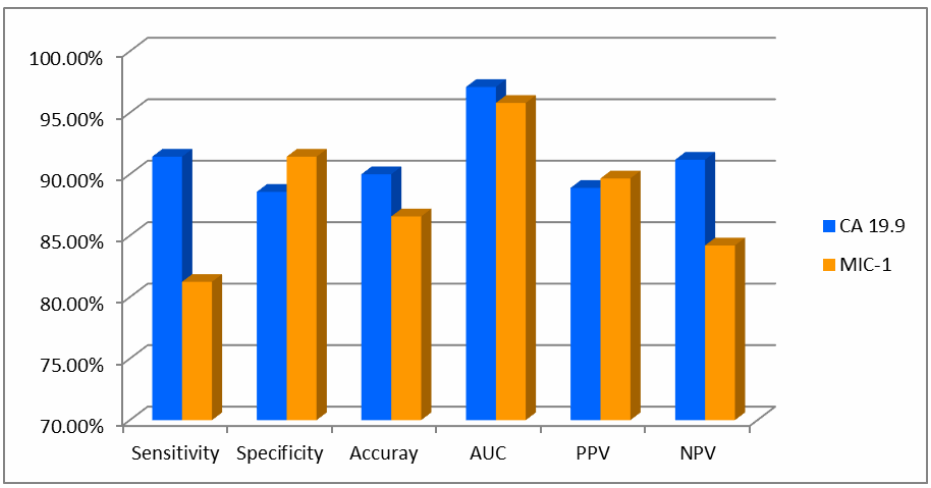

Fig 3: Overall comparative diagnostic performance of CA 19.9 and MIC-1 in PDAC

The diagnostic accuracy of CA 19.9 is found 90.00 % (95 % CI, 80.48% to 95.88%) and while that for MIC-1 is found 86.57 % (95 % CI, 76.03% to 93.67%).

IV. Discussion

Sensitivity is the proportion of true positive results out of all subjects with a disease selected for study. Thus, it is the ability of a test to yield a positive result for a subject that has that disease. On other hand, specificity is the proportion of true negative results out of all subjects who do not have a disease selected for study. In other words, it is the ability of the test to obtain normal range or negative results for a person who does not have that disease.[15,16,17]

In this study, we found CA 19.9 is more sensitive than MIC-1 (Sensitivity 91.43 % vs 81.25 %). While MIC-1 is more specific than CA 19.9 (Specificity 91.43 % vs 88.57 %) (Figure-3).

Jacob Shreffler and Martin R. Huecker denoted that sensitivity and specificity are inversely related: as sensitivity increases, specificity tends to decrease, and vice versa.[18] Our results match with opinion of Jacob Shreffler and Martin R. Huecker. In our result, CA 19.9 is more sensitive than MIC-1 but MIC-1 is more specific than CA 19.9.(Figure-3, Table-2)

Now, highly sensitive tests will lead to positive findings for patients with a disease, whereas highly specific tests will lead to finding of patients no disease.[18] Thus, sensitivity and specificity together provide a holistic picture of a diagnostic test. For a test to be novel marker, it should be highly sensitive as well as highly specific.

As per our study, comparing diagnostic efficacy of CA 19.9 (AUC = 0.971, accuracy = 90 %) and MIC-1(AUC = 0.958, accuracy = 86.57 %), it is found that both CA 19.9 and MIC-1 have nearly equal diagnostic accuracy. (Figure-3) Our results matches with meta-analysis done by Ying Yang et.al. in which they concluded that MIC-1 is a comparable biomarker to CA19–9 as an individual diagnostic tool for pancreatic cancer and each performs its own functions. (12) Further, we found that, positive predictive values of CA 19.9 and MIC-1 in PDAC are nearly equal. (Figure-3) On other hand, negative predictive values of CA 19.9 is higher than that of MIC-1.

Now, CA 19.9 is more sensitive than MIC. But CA 19-9 can be elevated in acute cholangitis, pancreatitis, obstructive jaundice and liver cirrhosis contributing to false positivity. Additionally, Lewis-negative blood type individuals not produce CA 19-9 levels, thus contributing to false negativity. This adds limitations in use of CA 19.9 alone as diagnostic tool for PDAC. On other hand, Jens Koopman et.al. in his study denoted that MIC-1 has ability to distinguish between pancreatic cancer and pancreatitis.[19] Further, MIC-1 it is more specific than CA 19.9. Thus, combination of CA 19.9 and MIC-1 may increase diagnostic efficacy in pancreatic ductal adenocarcinoma.

V. Conclusion

Our study found that, MIC-1 even being less sensitive can be a comparable biomarker to CA 19.9 due to high specificity and nearly equal accuracy to that of CA 19.9. Thus, combination of CA 19.9 and MIC-1 may increase diagnostic efficacy in pancreatic ductal adenocarcinoma.

Still worth exploration is required for diagnostic value of MIC-1 in combination with CA19.9 in diagnosis of PDAC.

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