# Clinical implication of serum CA125 for the prediction of malignancy in mucinous cystic neoplasms of the pancreas

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**Abstract.** Mucinous cystic neoplasms (MCNs) of the pancreas have malignant potential. Carbohydrate antigen 125 (CA125) is a common widely used biomarker for cancers. However, the role of CA125 in predicting the malignant change of MCNs is currently unidentified. Patients with resected and pathologically confirmed MCN were identified from a prospectively maintained database. The predictive role of serum CA125 in assessing malignant change of MCNs was analyzed and compared with serum carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA). This study included 164 patients with MCN (low/moderate grade, 153 cases; high grade and invasive, 11 cases). The serum levels of CA125 in the high grade and invasive group (45.1±42.1 U/ml) was significantly higher than those in the low/moderate grade group (21.0±46.2 U/ml, P=0.006). The area under the receiver operating characteristic (ROC) curve of CA125 (0.75) for predicting malignancy of MCNs was higher than that of CA19-9 (0.68) or CEA (0.72). The prediction value of CA125 was improved when combined with CEA (CA125 alone, sensitivity 36.4%, specificity 90.6%, accuracy 86.6%; combined with CEA, sensitivity 45.5%, specificity 88.2%, accuracy 85.0%). It was concluded that serum CA125 shows value in predicting the malignant change of MCNs, especially when combined with serum CEA.

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## Introduction

The mucinous cystic neoplasms (MCNs) of the pancreas are rare cystic tumors characterized by mucin production, presence of ovarian-type stroma, and malignant potential (1). It almost exclusively presents in middle-aged women and is located at the distal part of the pancreas (2). Unlike its mucinous producing counterpart intraductal papillary mucinous neoplasms (IPMNs), MCNs have no communication with either the main pancreatic duct or branch duct. Considering the possibility of malignant progression, surgical resection is usually recommended to MCNs (3,4). The prognosis of patients with invasive MCNs is much better than that of patients with invasive IPMNs, with a 10-year disease-specific survival of 79.6 vs. 27.2%, respectively (1).

Due to the invasive potential of MCNs, an accurate evaluation of malignant change is needed for appropriate clinical management (2). Variables including male sex, pancreatic head and neck location, increased tumor size, a solid component, and main pancreatic duct dilation have been reported to be positively associated with malignant change (5,6). Carbohydrate antigen 125 (CA125), carbohydrate antigen 19-9 (CA19-9), and carcinoembryonic antigen (CEA) are commonly used biomarkers for various types of cancers. Serum CA19-9 and CEA have been recommended to the management of pancreatic cyst diseases (4,7,8). However, the value of circulating CA19-9 and CEA in predicting MCN malignancy is limited. For example, a previous study showed that in 7 patients with pathologically confirmed severe dysplasia of mucinous cystic pancreatic neoplasms, 3 (42.9%) patients had an elevated circulating CA19-9 and 2 (28.6%) had an elevated circulating CEA (9). The study concluded that serum CA19-9 or CEA is not useful in screening mucinous cystic pancreatic neoplasm patients with malignancy (9). Although serum CA125 has been used in the management of various types of mucinous malignancies, its role in MCNs has not been identified.

In this study, by including 164 patients with resected and a histologic diagnosis of MCN, the predictive role of serum CA125 in assessing malignant change of MCNs was analyzed and compared with serum CA19-9 and CEA. In addition, the

values of CA125 combined with serum CA19-9 or CEA in evaluating malignant alteration were also examined.

## Patients and methods

*Patients and data collection.* All patients who underwent surgical resection of pancreatic MCN from May 2010 to November 2019 were identified from a prospectively maintained database of Fudan University Shanghai Cancer Center (Shanghai, China). All patients were pathologically verified to the diagnosis of MCN of the pancreas. Other pathological subtypes of pancreatic tumors including adenocarcinoma, serous cystic neoplasm, solid pseudopapillary tumor, and IPMN were excluded. Patients with previous or other concomitant cancer were also excluded. Clinicopathologic characteristics including age, sex, primary tumor location, cystic size, serum levels of CA19-9, serum levels of CEA, serum levels of CA125, and the operation type were collected. The recommended cutoff points based on the upper limit of the normal range were used (CA19-9, 37.0 U/ml; CA125, 35.0 U/ml; CEA, 5.2 ng/ml), as used in previous studies (8,10,11). This study was based on the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the Ethics Committee of Fudan University Shanghai Cancer Center. All patients provided informed consent for the use of their personal data for research purposes.

*Statistics.* Variables were presented as median (range) or mean ± standard deviation (SD), as appropriate. Comparisons of categorical variables were conducted with ranksum tests or Fisher's exact tests. Two-tailed t tests or ranksum test were used to compare parametric data. The ROC curve and the area under the ROC curve (AUC) were examined to determine the predictive value of biomarkers. Statistical analyses were conducted using Stata SE12.0 (StataCorp LP) and Prism statistical software (version 8; GraphPad Software, Inc.). P<0.05 was considered to indicate a statistically significant difference.

## Results

*Baseline characteristics.* The clinicopathologic characteristics of 164 patients with MCN are summarized in Table I. The female-to-male ratio was 11.6:1 and the median age was 48 years (range 18-82 years). Most of (91.5%) the primary tumors were located at the body and tail of the pancreas. All the patients underwent tumor resection and 86.6% of patients received distal pancreatectomy. The mean cyst size in diameter was 4.6 cm.

*Characteristics according to malignancy.* In this cohort, 6.7% (11/164) of patents were diagnosed with malignant MCNs (high grade and invasive). The cystic size in the high grade and invasive group (6.5±3.0 cm) was larger than that in the low/moderate grade group (4.5±2.8 cm, P=0.017). There was no statistical difference between the low/moderate grade group and the high grade and invasive group in age (P=0.384), sex (P=0.192), primary tumor location (P=0.294), and operation type (P=0.609).

*Tumor biomarker levels according to histological grade of dysplasia.* Serum levels of CA19-9, CEA, and CA125 in the low/moderate grade group and the high grade and invasive group are shown in Table II and Fig. 1. The serum levels of CA19-9 (309.2±423.2 vs. 49.0±198.3 U/ml, P=0.050), CEA (23.7±52.9 vs. 8.7±82.6 ng/ml, P=0.018), and CA125 (45.1±42.1 vs. 21.0±46.2 U/ml, P=0.006) in the high grade and invasive group was significantly higher than those in the low/moderate grade group. The area under the ROC curve of CA125 (0.75) for predicting malignancy of MCNs was higher than that of CA19-9 (0.68) or CEA (0.72, Fig. 2).

*Combining serum biomarkers in predicting malignancy of MCNs.* The sensitivity and specificity of CA125 as a biomarker in predicting malignancy of MCNs was 36.4% and 90.6%, respectively, with an accuracy of 86.6% when using 35 U/ml as the cut-off value (Table III). The accuracy of CA125 in predicting malignancy of MCNs was higher than CA19-9 (78.6%) and was comparable to CEA (91.7%) when using the recommended cut-off values. The prediction value was improved when combining CA125 with CEA (sensitivity 45.5%, specificity 88.2%, accuracy 85.0%).

## Discussion

The role of CA125 in predicting the malignant change of MCNs is currently unknown. In this study, by including 164 patients with MCN (low/moderate grade, 153 cases; high grade and invasive, 11 cases), the serum levels of CA125 in the high grade and invasive group (45.1±42.1 U/ml) was significantly higher than those in the low/moderate grade group (21.0±46.2 U/ml, P=0.006). The area under the ROC curve of CA125 (0.75) for predicting malignancy of MCNs was higher than that of CA19-9 (0.68) or CEA (0.72). The predicting value of CA125 was improved when combined with CEA (CA125 alone, sensitivity 36.4%, specificity 90.6%, accuracy 86.6%; combined with CEA, sensitivity 45.5%, specificity 88.2%, accuracy 85.0%). These results indicate that CA125 could be used to predict the malignant change of MCNs and the predictive value is improved when combined with CEA.

CA125, also called MUC16, is a commonly used biomarker for various types of malignancy, especially ovarian tumors (12). The role of CA125 in MCNs has been largely unconfirmed. Nagashio *et al* (13) collected cyst fluid from 68 patients with pancreatic cystic diseases to determine the application of cyst fluid analysis (CA125, CEA, CA19-9, amylase, and cytology) in differentiating pancreatic cystic lesions. They showed that cyst fluid CA125 concentrations may help to segregate MCNs (median, 1135.5 U/ml) from IPMNs (2 U/ml), serous cystic neoplasms (68.5 U/ml), and pseudocysts (6.5 U/ml), indicating the aberrant secretion of CA125 in MCNs (13). A multicentric retrospective study collected 347 patients with pancreatic MCN and found that CEA, CA19-9, and CA125 were remarkably different between the benign lesion group and the malignant lesion group (P<0.05) (14). However, none of these studies compared CA125 with CA19-9 or CEA. In this study, the area under the ROC curve of CA125 (0.75) for predicting malignancy of MCNs was higher than that of CA19-9 (0.68) or CEA (0.72), suggesting CA125 could be used to predict the malignant change of MCNs. Moreover, the predicting value of CA125 was improved when combined with CEA.

Table I. Baseline characteristics.

| Characteristics | Total (n=164) | Low/moderate grade (n=153) | High grade and invasive (n=11) | P-value |
|---|---|---|---|---|
| Age [median (range), years] | 48 (18-82) | 48 (18-75) | 58 (28-82) | 0.384[a] |
| Sex | | | | 0.192 |
| Female (%) | 151 (92.1) | 142 (92.8) | 9 (81.8) | |
| Male (%) | 13 (7.9) | 11 (7.2) | 2 (18.2) | |
| Location | | | | 0.294 |
| Head (%) | 14 (8.5) | 14 (9.2) | 0 (0.0) | |
| Body and tail (%) | 150 (91.5) | 139 (90.8) | 11 (100.0) | |
| Operation type | | | | |
| Distal pancreatectomy | 142 (86.6) | 131 (85.6) | 11 (100.0) | 0.609[b] |
| Enucleation | 9 (5.5) | 9 (5.9) | 0 (0.0) | |
| Middle segmental pancreatectomy | 2 (1.2) | 2 (1.3) | 0 (0.0) | |
| Pancreatoduodenectomy | 11 (6.7) | 11 (7.2) | 0 (0.0) | |
| Cyst size (mean ± SD, cm) | 4.6±2.9 | 4.5±2.8 | 6.5±3.0 | 0.017[a] |

[a]Ranksum test; [b]Fisher's exact test. SD, standard deviation.

Table II. Tumor biomarker levels according to the histological grade of dysplasia.

| Biomarker | Total (n=164) | Low/moderate grade (n=153) | High grade and invasive (n=11) | P-value |
|---|---|---|---|---|
| CA19-9 (mean ± SD, U/ml) | 67.0±228.7 | 49.0±198.3 | 309.2±423.2 | 0.050[a] |
| <37 (%) | 128 (80.5) | 121 (81.8) | 7 (63.6) | |
| ≥37 (%) | 31 (19.5) | 27 (18.2) | 4 (36.4) | |
| CEA (mean ± SD, ng/ml) | 9.8±80.9 | 8.7±82.6 | 23.7±52.9 | 0.018[a] |
| <5.2 (%) | 149 (94.9) | 141 (96.6) | 8 (72.7) | |
| ≥5.2 (%) | 8 (5.1) | 5 (3.4) | 3 (27.3) | |
| CA125 (mean ± SD, U/ml) | 22.8±46.2 | 21.0±46.2 | 45.1±42.1 | 0.006[a] |
| <35 (%) | 132 (88.6) | 125 (90.6) | 7 (63.6) | |
| ≥35 (%) | 17 (11.4) | 13 (9.4) | 4 (36.4) | |

[a]Ranksum test. CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CA125, carbohydrate antigen 125.
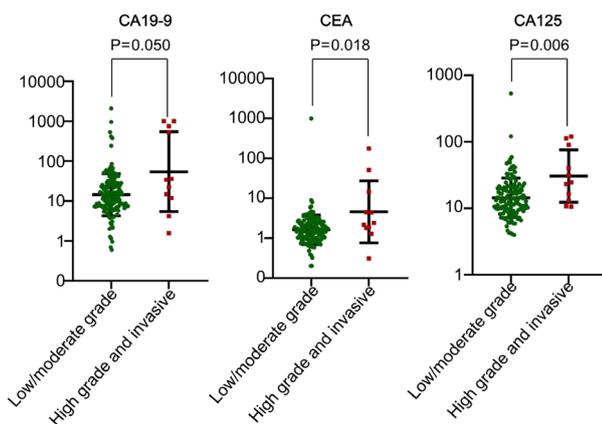


Figure 1. Individual serum levels of the three biomarkers (CA19-9, CEA, CA125) in the low/moderate grade group and the high grade and invasive group of patients studied. P-values of the three biomarkers are also reported. CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CA125, carbohydrate antigen 125.
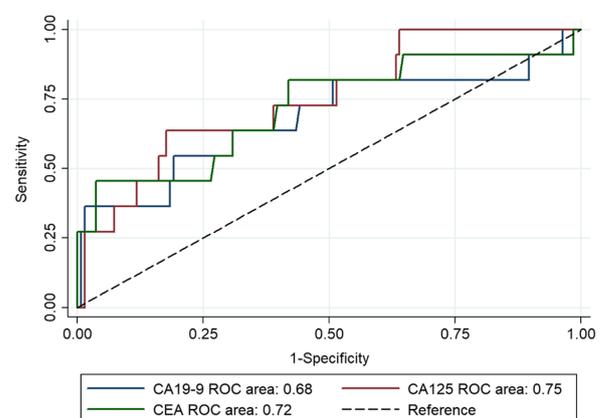


Figure 2. The ROC curve and area under the ROC curve for the three bio-markers (CA19-9, CEA, CA125) in predicting malignancy for MCNs. CA125 have higher prognostic value than other biomarkers. ROC, receiver operating characteristic; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CA125, carbohydrate antigen 125; MCNs, mucinous cystic neoplasms.

Table III. Diagnostic indices for CA19-9, CEA, and CA125 in predicting the malignant alteration of MCN.

| Value[a] | CA19-9 | CEA | CA125 | CA19-9 and/or CEA | CA19-9 and/or CA125 | CA125 and/or CEA |
|---|---|---|---|---|---|---|
| Sensitivity (%) | 36.4 | 27.3 | 36.4 | 54.5 | 54.5 | 45.5 |
| Specificity (%) | 81.8 | 96.6 | 90.6 | 78.8 | 75.2 | 88.2 |
| PPV (%) | 12.9 | 37.5 | 23.5 | 16.2 | 15.0 | 23.8 |
| NPV (%) | 94.5 | 94.6 | 94.7 | 95.8 | 95.4 | 95.2 |
| Accuracy (%) | 78.6 | 91.7 | 86.6 | 77.1 | 73.6 | 85.0 |

[a]Cut-off value, CA19-9, 37.0 U/ml; CEA, 5.2 ng/ml; CA125, 35.0 U/ml. PPV, positive predictive value; NPV, negative predictive value; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CA125, carbohydrate antigen 125; MCN, mucinous cystic neoplasm.

CA19-9, also termed as sialyl Lewis antigen a, is the best-validated biomarker for pancreatic adenocarcinoma (10,15). The biosynthesis of CA19-9 is affected by the Lewis antigen status (15). Lewis antigen negative individuals, accounting for 5-10% of the population, have no or low secretion of CA19-9 (15). CA19-9 has been recommended to assess the malignant change of pancreatic cyst tumors, including IPMNs and MCNs (3,5,7,16). Postlewait et al retrospectively identified 349 patients with MCN and demonstrated that patients with malignant neoplasms had a higher serum CA19-9 level than those without (median, 210 vs. 15 U/ml, P=0.001) (5). Zhao et al (17) showed that serum CA19-9 levels were significantly higher in malignant MCNs than in benign MCNs patients (P=0.026) for resected MCNs. Our study is consistent with previous findings, which finds that the serum levels of CA19-9 in the high grade and invasive group (309.2±423.2 U/ml) was significantly higher than those in the low/moderate grade group (49.0±198.3 U/ml, P=0.050), with an area under the ROC curve of 0.68.

CEA is a glycosylation biomarker which has been widely applied in the management of gastrointestinal malignancies (10). For pancreatic cyst tumors, cyst fluid CEA have been used to differentiate mucinous tumors (>192 ng/ml) from non-mucinous tumors (<5 ng/ml) (4,18). Brugge et al (19) showed cyst fluid CEA (optimal cut-off of 192 ng/ml, accuracy 79%) to be more useful than endoscopic ultrasound morphology (accuracy 51%) or cyst fluid cytology (accuracy 59%) for differentiating mucinous from nonmucinous cystic lesions. However, cyst fluid CEA has limited role in predicting malignancy or radiographic progression mucinous cysts of the pancreas (18). Several studies have also determined circulating CEA in predicting malignant MCNs (14,16,17). For example, Zhao et al (17) demonstrated that serum CEA levels were significantly higher in malignant MCNs than in benign MCNs patients (P=0.005) for 82 patients with resected MCNs. In this study, the serum levels of CEA in the high grade and invasive group (23.7±52.9 ng/ml) was significantly higher than those in the low/moderate grade group (8.7±82.6 ng/ml, P=0.018), with an area under the ROC curve of 0.72. Our study confirms previous findings that CEA could be used to predict malignant MCNs.

In summary, CA125 shows promising value in predicting malignant MCNs. Its predictive value may be strengthened by combining with CEA. However, further evidence, especially evidence from multicentric, large sample size, and/or prospective studies is needed to confirm the findings.

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Authors' contributions

GL, CL, XY designed the study. SD, ZF, YG, HC, KJ, YQ, ZX, YL, RW, YZ, QN, XY, CL and GL collected and analyzed data. GL wrote the draft. XY and CL revised it critically. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

The study protocol was approved by the ethics committee of Fudan University Shanghai Cancer Center.

## Patient consent for publication

Written informed consent was acquired from all of the subjects enrolled.

## Competing interests

The authors declare that they have no competing interests.

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