Proposed cut-off value of CA19-9 for detecting pancreatic cancer in patients with diabetes: a case-control study

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Abstract. Pancreatic cancer is a highly lethal malignancy. CA19-9 is a well-known marker for diagnosis of pancreatic cancer, but the serum CA19-9 level is reported to be elevated in patients with poorly controlled diabetes. This study evaluated the sensitivity, specificity, and cut-off value of serum CA19-9 for detection of pancreatic cancer in patients with diabetes. A case-control study of 236 patients was performed. The case group was selected from diabetic patients with pancreatic cancer, while one control was selected for each case from among diabetic patients without pancreatic cancer during the same period. The case group \( (n = 118) \) and the control group \( (n = 118) \) were matched for age, sex, and pancreatic cancer risk factors. Receiver operating characteristic (ROC) curves were plotted to determine the serum CA19-9 level that predicted pancreatic cancer. Then the sensitivity and specificity of CA19-9 were calculated for the threshold value. There were no significant differences of age, sex, BMI, smoking, alcohol intake, and HbA1c between the case and control groups. According to ROC analysis, a serum CA19-9 level of 75 U/mL had the maximum sensitivity and specificity for separating diabetic patients with or without pancreatic cancer. Using this cut-off value, the sensitivity and specificity of CA19-9 for pancreatic cancer was 69.5% and 98.2%, respectively, while the area under the ROC curve was 0.875 [95%CI: 0.826–0.924]. We propose that a serum CA19-9 level of 75 U/mL should be used as the cut-off value when screening patients with diabetes for pancreatic cancer.

Key words: Diabetes mellitus, CA19-9, Pancreatic cancer, Cut-off value, Case-control study

Materials and Methods

This was a case-control study of 236 subjects admitted...
to St. Marianna University Hospital between April 2007 and March 2017. Demographic characteristics and other information were extracted from the electronic medical records. The case group was selected from among patients with diabetes and pancreatic cancer diagnosed by gastroenterologists. Patients were defined as having diabetes if they were taking antidiabetic agents for previously diagnosed diabetes or if HbA1c was ≥6.5%, fasting blood glucose was ≥126 mg/dL, or postprandial plasma glucose was ≥200 mg/dL in patients not on antidiabetic treatment. For each case, one control was selected from among patients managed at the diabetes center of St. Marianna University Hospital during the same period. Patients were excluded if they had other malignancies or diseases that could increase the CA19-9 level, such as interstitial pneumonia. The case group (n = 118) and the control group (n = 118) were matched for age, sex, and risk factors for pancreatic cancer (BMI, HbA1c, smoking, and alcohol intake). Serum CA19-9 was measured with a fully automated LumiPulse Presto assay kit (Fujirebio Inc., Tokyo, Japan) based on a chemiluminescent immunoassay [12].

This study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of St. Marianna University School of Medicine.

Statistical analysis

Receiver operating characteristic (ROC) curves were plotted to determine the optimum serum CA19-9 level for predicting pancreatic cancer. Then the sensitivity and specificity of CA19-9 were calculated for the threshold value. Categorical variables were expressed as numbers or percentages. Continuous variables with a normal distribution were reported as the mean ± SD, while skewed variables were displayed as the median with interquartile range. The Shapiro-Wilk normality test was used to assess whether variables had a normal distribution. Between-group differences of normally distributed data were assessed by using a two-tailed unpaired t-test, while differences of non-normally distributed data were evaluated with the Mann-Whitney U test. Differences were considered to be significant if the probability value (p) was less than 5%. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) and the graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), a modified version of R commander with statistical functions frequently employed in biostatistics.

Results

The 118 patients with diabetes and pancreatic cancer in the case group included 76 men and 42 women aged from 58 to 88 years (mean age: 71.1 ± 8.9 years). The 118 patients in the control group had diabetes without pancreatic cancer, including 77 men and 41 women aged from 47 to 89 years (mean age: 70.3 ± 8.6 years). There were no significant differences of age, sex, BMI, smoking, alcohol intake, and HbA1c between the case group and the control group (Table 1). The serum CA19-9 level was significantly higher in the case group than in the control group (p < 0.001), since the median serum CA19-9 level was only 15 U/mL in the control group without pancreatic cancer versus 370 U/mL in the case group with pancreatic cancer. The duration of diabetes was significantly shorter in the case group than in the control group (8.0 ± 9.1 vs. 14.5 ± 11.9 years; p < 0.001), while the glycoalbumin (GA) level was significantly higher in the case group than in the control group (32.5 ± 7.8 vs. 27.6 ± 8.0%; p < 0.001) (Table 1).

As shown in Fig. 1A, there was a weak positive correlation between HbA1c and the serum concentration of CA19-9 (logarithmically transformed) in the control group (r = 0.227, p = 0.015). A weaker positive correlation (r = 0.197, p = 0.043) was also observed between GA and the CA19-9 (Fig. 1B). ROC analysis showed that the area under the ROC curve (AUC) was 0.875 [95%CI: 0.826–0.924] and the cut-off value of serum CA19-9 that demonstrated the maximum sensitivity and specificity for separating patients with or without pancreatic cancer was 75 U/mL (83.9% vs. 82.2%, respectively). This cut-off value showed a higher diagnostic accuracy for pancreatic cancer than the conventional standard value of 37 U/mL (83.9% vs. 82.2%, respectively).

Discussion

In the present study, the case group and the control group were completely matched with respect to age, sex, and pancreatic cancer risk factors such as BMI, HbA1c, smoking, and alcohol intake. However, the duration of diabetes was significantly shorter in the case group than in the control group (Table 1). Although HbA1c was similar in both groups, GA (which reflects the mean blood glucose level during the previous two weeks) was
significantly higher in the case group, suggesting rapid
deterioration of glycemic control due to pancreatic can‐
cer [13].

There was a weak positive correlation between HbA1c
and the logarithmically transformed CA19-9 in the con‐
trol group, consistent with previous reports on patients
with type 2 diabetes [14, 15]. When the subgroup of 15
(12.7%) control patients with a serum CA19-9 level
exceeding 37 U/mL despite not having pancreatic cancer
was investigated in detail, no features were associated
with elevation of CA19-9 apart from poor glycemic con‐
trol (data not shown). Although the mechanism remains
unclear, a longer half-life may contribute to elevation of
serum CA19-9 levels in patients with diabetes [15].

ROC analysis showed that the AUC was 0.875
[95%CI: 0.826–0.924], and 75 U/mL was the cut-off
value of serum CA19-9 with the maximum sensitivity
and specificity for identifying patients who had pancre-
atic cancer. Using this cut-off value, the sensitivity and specificity of CA19-9 for detecting pancreatic cancer was 69.5% and 98.2%, respectively. The cut-off value of 75 U/mL showed a higher diagnostic accuracy than the conventional standard value of 37 U/mL (83.9% vs. 82.2%, respectively).

In our control group without pancreatic cancer, only two patients had a CA19-9 level >75 U/mL. Therefore, when CA19-9 exceeds 75 U/mL, the probability of pancreatic cancer is high and detailed investigations should be performed.

ROC analysis to ascertain the optimal cut-off value is based on the trade-off between sensitivity and specificity. The higher cut-off value of 75 U/mL would result in an increase of false-negatives. It has been reported that an elevated serum levels of CA19-9 in patients with diabetes were decreased within 2 weeks by improvement of glycemic control [10, 15, 16]. Therefore, when serum CA19-9 is between 37 and 75 U/mL, it would seem reasonable to re-examine the patient at least 2 weeks after improvement of glycemic control to avoid both unnecessary investigations and overlooking pancreatic cancer.

This study had several limitations. First, CA19-9 is expressed by the exocrine pancreas and the serum CA19-9 level is also elevated in patients with diseases other than pancreatic cancer, such as upper gastrointestinal tract cancer, ovarian cancer, hepatocellular cancer, and colorectal cancer [4, 15]. Although we excluded patients who were known to have any of these diseases from the control group, we may have missed some undiagnosed cases. Thus, underlying comorbidities could potentially have influenced our findings.

Second, it has been reported that CA19-9 gives false-negative results in patients who are Lewis blood group-negative [Le (a-b-)] [17], because these individuals cannot synthesize sialyl Lea (CA19-9) [5]. Approximately 5–10% of the Japanese population is Le (a-b-) [15]. Even though none of the subjects in the present study had undetectable CA19-9 levels, if CA19-9 is below 1.2 U/mL in a patient, the test should be considered non-informative and other tumor makers should be investigated.

In conclusion, we propose that the cut-off value of serum CA19-9 should be set at 75 U/mL when screening patients with diabetes for pancreatic cancer. A positive result should encourage clinicians to perform detailed investigations to detect pancreatic cancer, such as contrast CT, pancreatic endoscopic ultrasound, or magnetic resonance cholangiopancreatography, rather than relying on simpler tests such as abdominal ultrasonography. If the serum CA19-9 level is between 37 and 75 U/mL in a patient with diabetes, re-examination after improvement of glycemic control is recommended before deciding whether to perform investigations for pancreatic cancer.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.
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