Serum Carbohydrate Antigen (CA) 19-9 of Pancreatic Solid Mass Patients in Dr. Cipto Mangunkusumo National Central General Hospital

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ABSTRACT

Background: *Pancreatic cancer is a lethal disease associated with poor prognosis. Carbohydrate antigen (CA) 19-9 is one of the elevated tumor markers in pancreatic cancer. However, data regarding CA 19-9 serum levels in pancreatic cancer in Indonesia is still scarce. This study aims to evaluate the clinical use of CA 19-9 in pancreatic cancer patients in Dr. Cipto Mangunkusumo National Central General Hospital.*

Method: *This study is a cross-sectional study that served data of demographic information, CA 19-9 level, tumour, node, metastasis (TNM) stage, site, histopathology, and resectability of pancreatic cancer. This study included 77 subjects. The data were collected from electronic medical records and registered data of patients in the Gastrointestinal Endoscopy Center, Dr. Cipto Mangunkusumo National Central General Hospital, Jakarta between 2014 to 2019. Sensitivity and specificity analysis of CA 19-9 were performed using the receiver operating characteristic (ROC) curve.*

Results: *We found 77 pancreatic cancer patients with a mean age of 54.2±10.4 years old. Most of them were males (59,7%), were found at stadium IV (41,6%) and unresectable tumor (68,8%). Non-adenocarcinoma which was mainly found in the head of the pancreas (76,6%) were confirmed in 67,5% of patients. The sensitivity and specificity of CA-19 9 to diagnose adenocarcinoma pancreas were 32% and 62% (p=0.939).*

Conclusion: *CA 19-9 should be used in aiding diagnosis, in conjunction with other modalities, such as radiological procedures and histopathology results. Measuring serum CA19-9 level in the early diagnosis could guide clinicians in determining the treatment and prognosis of pancreatic cancer.*

Keywords: *carbohydrate antigen (CA)19-9, adenocarcinoma pancreas, bilirubin, resectability*

ABSTRAK

Latar belakang: *Kanker pankreas merupakan penyakit yang mematikan yang berhubungan dengan prognosis yang buruk. Carbohydrate antigen (CA) 19-9 merupakan salah satu penanda tumor yang meningkat pada kanker pankreas. Namun, data mengenai kadar CA 19-9 pada serum pada kanker pankreas di Indonesia masih jarang. Penelitian ini bertujuan untuk mengevaluasi manfaat klinis CA 19-9 pada pasien kanker panrkeas di Rumah Sakit Umum Pusat Nasional Dr. Cipto Mangunkusumo.*

Metode: *Penelitian ini merupakan penelitian potong lintang yang menyajikan data mengenai informasi demografis, kadar CA 19-9, stadium tumour, node, metastasis (TNM), lokasi, histopatologi, dan resektabilitas kanker pankreas. Penelitian ini melibatkan 77 subjek penelitian. Data dikumpulkan dari rekam medis elektronik*

dan register pasien di Pusat Endoskopi Gastrointestinal, Rumah Sakit Umum Pusat Nasional Dr. Cipto Mangunkusumo antara 2014 hingga 2019. Analisis sensitivitas dan spesifistas CA 19-9 dilakukan emnggunakan kurva ROC.

Hasil: *Terdapat 77 pasien kanker panrkeas dengan rata-rata usia 54.2±10.4 tahun. Sebagian besar dari pasien adalah laki-laki (59,7%), pada stadium IV (41,6%) dan tumor yang tidak dapat direseksi. (68,8%). Kanker non-adenokarsinoma yang paling sering ditemukan pada kaput pankreas (76,6%) ditemukan pada 67,5% pasien. Sensitivitas dan spesifistas CA 19-9 untuk mendiagnosis adenokarsinoma pankreas adalah 32% dan 62% (p=0.939).*

Simpulan: *CA 19-9 dapat digunakan untuk membantu diagnosis, bersamaan dengan modalitas-modalitas lain, seperti pemeriksaan radiologi dan histopatologi. Pengukuran kadar CA 19-9 serum pada awal diagnosis dapat membantuk klinisi untuk menentukan tata laksana dan prognosis kanker pankreas.*

Kata kunci: *carbohydrate antigen (CA) 19-9, adenokarsinoma pankreas, bilirubin, resektabilitas*

INTRODUCTION

Pancreatic cancer is a highly lethal disease associated with poor prognosis. Despite improvements in the survival rates for other major cancer forms, pancreatic cancer survival rates have remained relatively unchanged for 50 years.[1,2] To date, pancreatic cancer is still the fourth leading cause of cancer-related mortality for women and men. Its 5-year survival rate is less than 5.5%, and the majority of the patients do not survive within 2 years from diagnosis.[3] Approximately 338000 new cases of pancreatic cancer are diagnosed annually.[4] This poor prognosis is attributable to the late-stage presentation, lack of effective treatments, early recurrence, and absence of clinically useful biomarkers which can detect pancreatic cancer in its precursor forms or earliest stages.[5]

CA 19-9 is one of the biochemical tumor markers reported to be elevated in patients with pancreatic cancer.[6] It is synthesized by a variety of cells located throughout the gastrointestinal tract such as pancreatic, biliary, gastric, colonic, and salivary epithelial cells. Normal serum levels of CA-19 9 ranges from 0 to 37 U/ml. It is the only serum marker for pancreatic cancer that has been used in clinics. It has a sensitivity and specificity of around 80%.[2] CA 19-9 is the most commonly used and the best-validated serum tumor marker for pancreatic cancer diagnosis. It exhibits a dramatic increase in its plasmatic levels during neoplastic disease.[7]

Although CA 19-9 remains the only pancreatic cancer marker widely used, its utility has some limitations. CA 19-9 should not be solely used to diagnose pancreatic cancer. It could assist to diagnose pancreatic cancer in conjunction with radiology and histopathology examinations. CA 19-9 has several critical aspects for its clinical use, such as false-negative results in subjects with Lewis $^{a-b-}$ genotype and false-positive elevation in patients with benign disease.[7] The data regarding CA 19-9 serum levels in pancreatic cancer in Indonesia is still scarce. This study aims to evaluate the clinical use of CA 19-9 in pancreatic cancer patients in Dr. Cipto Mangunkusumo National Central General Hospital.

METHOD

This study was a cross-sectional study. Data were collected from electronic medical records and registered data of patients from 2014 to 2019 in the Gastrointestinal Endoscopy Center, Dr. Cipto Mangunkusumo National Central General Hospital. There were 77 subjects included in this study. Incomplete data were collected manually through patients' medical records. Pancreatic cancer subjects who had CA 19-9 serum laboratory results were included. Patients' serum CA 19-9 level was measured using a standard immunofluorescence laboratory method.

Patients' demographic information, CA 19-9 level, TNM stage, site, histopathology, and resectability were analyzed by IBM SPSS version.20. The exact Fisher test or Chi-square test was used for statistical analysis in identifying the association between histopathology of pancreatic cancer, bilirubin serum levels, resectability of pancreatic cancer, and CA 19-9 levels. P-values of less than 0.05 was considered statistically significant. The sensitivity and specificity of the CA 19-9 level in the diagnosis of adenocarcinoma were evaluated from the ROC curve.

RESULTS

This study included 77 subjects with a mean age of 54.2±10.4 years old, as shown in table 1. The total serum bilirubin level in early diagnosis was 14.2±13.4 mg/dL. The unresectable tumor was found in 68.8

% of subjects. The majority of the tumor was found in the head of the pancreas (76.6%). Histopathology examination revealed that 32.5% of subjects were positive for adenocarcinoma and 67.5% of subjects were negative for adenocarcinoma. Table 1 shows the characteristics of the patients.

Table 1. Characteristics of the patients

Demography	Results, n (%)
Age (mean)	54.2±10.4 years
Sex	
Male	46 (59.7)
Female	31 (40.3)
Bilirubin (mean)	14.2±13.4 mg/dL
CA 19-9	325.3 U/L (1.3-80626)
Stage	
I	9 (11.7)
II	14 (18.2)
III	22 (28.6)
IV	32 (41.6)
Resectable	24 (31.2)
Unresectable	53 (68.8)
Histopathology	
Adenocarcinoma	25 (32.5)
Non-adenocarcinoma	52 (67.5)
Tumor location	
Head	59 (76.6)
Body	7 (9.1)
Tail	3 (3.9)
Ductal	8 (10.4)

Table 2 shows the results of CA 19-9 found in the different histological groups. Patients with adenocarcinoma had a higher level of CA 19-9 serum than non-adenocarcinoma.

Table 3 shows the histopathology group subdivided according to CA 19-9 and bilirubin levels. We found a positive trend toward higher bilirubin serum and CA 19-9 levels, although this result was not statistically significant (p 0.145).

Table 4 shows that CA 19-9 serum levels > 37 U/L was found higher in the unresectable tumor group. A non-statistically significant result was also found in this parameter.

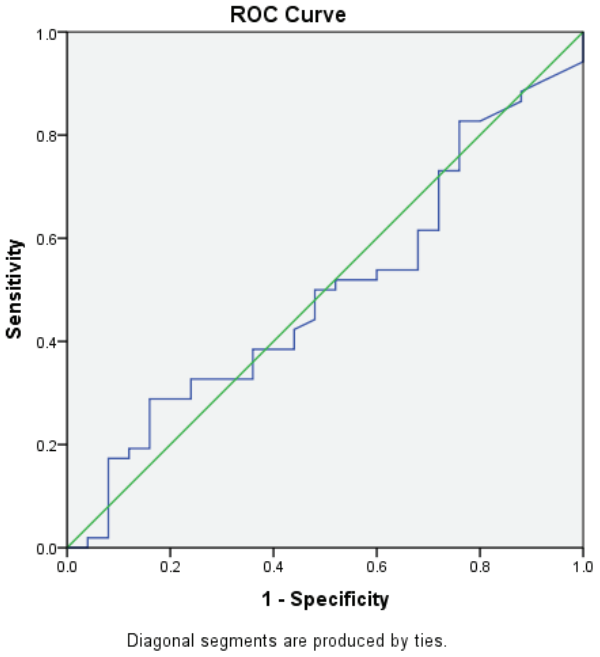

Figure 1. ROC Curve of CA 19-9 serum levels in pancreatic cancer

The ROC curve demonstrated in Figure 1 shows that CA 19-9 was an inadequate marker to differ adenocarcinoma and non-adenocarcinoma pancreas (p=0.939). The best sensitivity and specificity to diagnose adenocarcinoma pancreas were 32% and 62% respectively with a cut-off point of 1303.

DISCUSSION

Pancreatic cancer remains a deadly disease with a very poor 5 years survival rate which is only 8%. The poor survival rate is attributed to several factors. The most important thing is the absence of an ideal screening method for pancreatic cancer, and most of the patients are diagnosed in the later stage. It becomes a challenge for many clinicians and researchers to find

Table 2. Histopathology of pancreatic cancer and CA 19-9 levels

Histopathology	Total subjects	Median of CA 19-9	Range of CA 19-9	CA 19-9 >37 U/L, n (%)	P
Adenocarcinoma	25	325.3	8-80626.00	18 (72)	0.939
Non-adenocarcinoma	52	307.7	1.3-43378.00	32 (61)	

Table 3. CA 19.9 serum levels in the different groups studied, subdivided according to bilirubin serum levels.

Histopathology	Tb ≤ 2 CA 19-9 > 37	Tb > 2 CA 19-9 > 37	P
Adenocarcinoma	0	18	0.145
Non-adenocarcinoma	3	28	

Tb : Total bilirubin serum

Table 4. The association between resectability of pancreatic cancer and CA 19-9 serum levels

	CA 19-9 ≤ 37	CA 19-9 > 37	P
Resectable	11	13	0.132
Unresectable	15	38	

an ideal screening tool, so the patients can be diagnosed in earlier stage.[7]

In asymptomatic individuals, the role of CA 19-9 serum levels as a screening tool had been extensively evaluated, but unfortunately, it had no utility as a screening marker given its very low predictive value. Moreover, when many pre-invasive pancreatic lesions were detected by imaging, serum CA 19-9 levels were often normal. So it should not be used as a screening modality in asymptomatic patients.[7]

Some scientific publications had been carried out on the diagnosis accuracy of CA 19-9 in pancreatic cancer patients. Duffy et al reviewed 37 U/L as a cut-off point of CA 19-9 levels to be most accurate for discriminating pancreatic cancer from benign pancreatic disease. This study showed 81% and 90% of sensitivity and specificity respectively, to diagnose pancreatic cancer. Another study by Goonetilleke et al, showed 79% sensitivity and 82% specificity of CA 19-9 to diagnose pancreatic cancer.[6] In this study, we used CA 19-9 levels to differ adenocarcinoma pancreas and other solid pancreatic cancers.

The incidence of pancreatic cancer predominantly increased after the age of 55 years old. In our study, we found a similar result where the median age of pancreatic cancer patients was 54 years old. Siegel et al proposed age was an important risk factor for the development of pancreatic cancer. The incidence rate of pancreatic cancer among patients older than 65 years was 66.4%, while the incidence among patients older than 80 years was 91.1%.[8,9]

The incidence of pancreatic adenocarcinoma for a long period was higher in men than in women, but in the last decades, the numbers had become more even, today there is no longer any evidence of a sex-related difference.[10] This similar result was also found in our study. Other risk factors for adenocarcinoma pancreas were a family history of pancreatic cancer, cigarette smoking, African-American origin, Helicobacter pylori infection, and gene mutations (KRAS, BRCA2, TP53, and SMAD4).[5]

The presence of higher bilirubin levels could significantly increase CA 19-9 levels, in both benign and biliary disease malignancy. Consequently, the sensitivity and specificity of CA 19-9 at the cut-off level of 37 IU/mL decreased.[11] In this study, the ROC curve showed no significant result of CA 19-9 to evaluate pancreatic cancer, especially to differ adenocarcinoma and non-adenocarcinoma tumors. With low sensitivity and specificity, CA 19-9 levels were not established as serum markers for diagnosing adenocarcinoma pancreas in our settings.

The majority of pancreatic cancer sites in our study were the head of the pancreas.[12] Pancreatic cancer in the body and tail of the pancreas have more aggressive tumor biology compared to pancreatic cancer in the head of the pancreas.[13] Approximately 65% of pancreatic cancer occurred in the head of the pancreas whereas 50% occurred in the body and tail of the pancreas. We also found that the majority of cancer in our patient was located in the head of the pancreas. Studies had shown no difference in CA 19-9 sensitivity between tumors in the head and those found in the body-tail region of the pancreas.[11]

Nine studies investigated the association between the accuracy of tumor markers CA 19-9 and tumor stage.[6] In all studies, tumor marker sensitivity was greater in the more advanced stage of cancer than in the initial presentation. In this study, the unresectable stage of the tumor was found in a higher trend of CA 19-9 serum.

This study is the first study investigating CA 19-9 serum levels in Indonesia, although it has some limitations. Besides its small subject number, there is no follow up of CA 19-9 data. As mentioned earlier, the elevation of bilirubin in obstructive jaundice could affect the sensitivity and specificity of CA 19-9 levels. This study does not explain other types of malignancies due to a lack of data.

CONCLUSION

In summary, while CA 19-9 is the most commonly used tumor marker in pancreatic cancer, it has a low sensitivity and specificity. CA 19-9 should be used in aiding diagnosis, in conjunction with other modalities, such as radiological procedures and histopathology results.

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