

6-26-2021

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Recommended Citation

Pasihulizan, Pasihulizan and Putranto, Agi S. (2021) "Preoperative CA 19-9 Level as Additional Predictor of Pancreatic Head Adenocarcinoma Resectability," *The New Ropanasuri Journal of Surgery*. Vol. 6 : No. 1 , Article 1.

DOI: 10.7454/nrjs.v6i1.1099

Available at: <https://scholarhub.ui.ac.id/nrjs/vol6/iss1/1>

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Preoperative CA 19-9 Level as Additional Predictor for Resectable Pancreatic Head Adenocarcinoma

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Corresponding author: pasihulizan@gmail.com Received: 05/Dec/2020 Accepted: 05/Apr/2021 Published: 26Jun/2021

Website: <https://scholarhub.ui.ac.id/nrjs/> DOI:10.7454/nrjs.v6i1.1099

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Abstract

Introduction. Determining eligibility criteria for resection is the basis of pancreatic head adenocarcinoma treatment planning, yet the currently used CT scan only has 80% accuracy as its primary modality. This study aimed to investigate preoperative CA 19-9 level use to help predict resectability of pancreatic head adenocarcinoma.

Method. Determining eligibility criteria for resection is the basis of pancreatic head adenocarcinoma treatment planning, yet the currently used CT scan only has 80% accuracy as its primary modality. This study aimed to investigate preoperative CA 19-9 level use to help predict resectability of pancreatic head adenocarcinoma.

Results. There were 54 subjects enrolled in the study, with the Mean age of both unresectable and resectable subjects is 53.78 ± 11.13 years. Twenty-nine were assigned as an unresectable group and 25 subjects as a resectable group. We found significant differences in CA 19-9 serum albumin levels and Kamofsky score between the resectable and unresectable groups. The cut-off point for CA 19-9 levels was 140.65 U/mL, with a sensitivity of 82.76% (64.23% -94.15%), specificity of 72.00% (50.61% -87.93 %), and AUC of 0.784.

Conclusion. CA 19-9 was significantly associated with eligibility criteria for pancreatic head carcinoma resection. CA 19-9 has a good diagnostic value as an additional predictor for resectable pancreatic head carcinoma.

Key words: CA 19-9, eligibility criteria for resection, resectable pancreatic head adenocarcinoma

Introduction

Pancreatic head adenocarcinoma is the eleventh highest cause of cancer mortality which causes 4.5% of all cancer deaths globally. In Indonesia, pancreatic head adenocarcinoma recorded 4.812 deaths from a total of 4.940 cases in 2018. Surgery is the primary treatment choice for pancreatic head adenocarcinoma, both for complete resection and as a primary measure before supportive therapy. Surgery planning for each case heavily relies on determining the eligibility criteria for adenocarcinoma resection. These cases were assigned as resectable, borderline, and unresectable, then later given a treatment plan.¹⁻⁴

Computerized tomography (CT) scan is currently the most used modality to determine eligibility criteria for pancreatic head adenocarcinoma resection through finding the involvement of arteries and veins in the tumor. This modality shows pancreatic head adenocarcinoma detection ability with a wide range of sensitivity and specificity of 70-100%. However, CT scans had limitations, which are low effectivity in detecting occult peritoneal carcinomatosis, <1 cm liver metastasis, and occult vascular involvement. These limitations call for an additional effective modality to assist surgeons in determining eligibility criteria for pancreatic head adenocarcinoma resection.⁵⁻⁸

Carbohydrate Antigen 19-9 (CA 19-9) is a serum tumor marker produced by pancreatic cancer exocrine cells, which are detected in the pancreatic, hepatic, biliary tract, gastric, and ovarium carcinomas. Although it is not a specific tumor marker, some studies showed that CA 19-9 is helpful for prognostic uses. Including predicting the diagnosis of resectable pancreatic head adenocarcinoma. A study by Killic et al. showed that CA 19-9 of 256.6 U/dL referred to an indicator of unresectable adenocarcinoma, despite CT scan findings.⁶ However,

Wiguna et al. found the CA 19-9 of 126.76 U/mL as the cutoff level for resectability, with a sensitivity of 76.9% and specificity of 80%.⁵

The procedure of treatment relies on being resectable and operable or not. The resectability is determined by tumor vascularization and the presence of metastasis. While as, an operable pancreatic head adenocarcinoma is determined by the patients' performance status and laboratory indicator on the Pitts score. These indicators determine whether the procedure would be intense curative or palliative. Our focus of interest in this study is to diagnose resectable pancreatic head adenocarcinoma based on a CT scan. This study aimed to add more evidence on preoperative CA 19-9 level potential as a predictor for resectable pancreatic head adenocarcinoma. We also analyzed and further investigate other patient characteristics that may aid in determining eligibility criteria for pancreatic head adenocarcinoma resection.

Method

A cross-sectional study was conducted using the data of all pancreatic head adenocarcinoma patients in dr. Cipto Mangunkusumo Hospital enrolled through 2015-2020. The inclusion criteria were those aged ≤ 65 years, diagnosed histopathologically or by CT imaging, and have preoperative CA 19-9. A minimum sample size of 49 was calculated using descriptive categoric sample formula, and 54 samples were enrolled to avoid inadequate sample size due to dropout.

We collected data from medical records, including age, gender, body weight, body height, body mass index (BMI), comorbidity, CA 19-9 levels, Karnofsky performance score, Subjective Global Assessment (SGA) based on Canadian malnutrition task force score, albumin levels, bilirubin levels, vascular involvement in tumor determined from CT scan, resectable or unresectable diagnosis assigned by surgeons in

charge, histopathological findings, and surgery chosen by surgeons in charge.

All numeric variable was evaluated for distribution normality using Kolmogorov-Smirnov Test. Bivariate analysis tests were conducted according to data type and distribution normality using the Unpaired T/Mann-Whitney test between resectable and unresectable pancreatic head adenocarcinoma groups. We carried out further diagnostic analysis for CA 19-9 levels, and the ROC curve was used to determine the cutoff point. A Chi-square test was used for this purpose. Bias control was done using multivariate logistic regression analysis of factors with $p < 0.25$ on bivariate analysis.

This study approved by Ethical Committee of Faculty of Medicine, Universitas Indonesia, No. KET-1222/UN2.F1/ETIK/PPM.00.02/2020.

Results

Patient characteristics and diagnostics modalities findings bivariate analysis

This study included 54 subjects diagnosed with pancreatic head adenocarcinoma enrolled in dr. Cipto Mangunkusumo General Hospital through 2016-2020. Twenty-nine subjects were assigned as an unresectable and 25 subjects as a resectable group through CT scan imaging. Demographic characteristics, surgical approach is chosen; laboratory, imaging, and histopathological findings of subjects are shown in Table 1. The mean age of both unresectable and resectable subjects is 53.78 ± 11.13 years old.

Table 1. Characteristics of subjects with pancreatic head adenocarcinoma in the study

	Unresectable (n= 29)	Resectable (n= 25)	p
Age (mean ± SD)	53.83±10.89	53.72±11.62	0.851
Gender [n (%)]			0.625
Male	17 (58.62%)	13 (52%)	
Female	12 (41.38%)	12 (48%)	
Weight in kg (mean ± SD)	53.98±12.39	54.52±8.64	0.277
Height in kg (mean ± SD)	162.55±7.14	160.40±7.22	0.972
Kamofsky score [median (min-max)]	80 (50-100)	100 (60-100)	<0.001
BMI [n (%)]			0.003
Underweight	14 (48.28%)	2 (8%)	
Normoweight	14 (48.28%)	22 (88%)	
Overweight	1 (3.45%)	1 (4%)	
Diabetes Mellitus [n (%)]	2 (6.70%)	4 (16%)	0.399
Scored SGA [n (%)]			<0.001
A: well-nourished	6 (20.69%)	20 (80%)	
B: mild/moderately-nourished	19 (65.52%)	3 (12%)	
C: severely malnourished	4 (13.79%)	2 (8%)	
Bilirubin in mg/dL [median (min-max)]			
Total	7.02 (0.33-31.21)	7.40 (0.34-30.00)	0.938
Direct	5.40 (0.17-22.40)	5.40 (0.20-24.90)	0.896
Indirect	1.18 (0.12-8.81)	2.08 (0.10-17.20)	0.259
CA 19-9 level in U/mL [median (min-max)]	421.9 (25.75-42.648)	65 (12-12.000)	<0.001
Albumin in g/dL [median (min-max)]	3.00 (2.30-4.90)	3.37 (2.53-4.41)	0.030
Vascular involvement [n (%)]			
No involvement	10 (34.48%)	23 (92%)	
SMV	10 (34.48%)	2 (12%)	
SMA	3 (10.34%)	0	<0.001
CHA	1 (3.45%)	0	
CT	1 (3.45%)	0	
SMA + SMV	3 (10.34%)	0	
Metastasis [n (%)]	14 (48.28%)	0	<0.001
Surgery [n (%)]			
Biliary stent only	11 (37.93%)	8 (32%)	
Whipple	0	10 (40%)	
Hepaticojejunostomy bypass	1 (3.45%)	1 (4%)	
Double bypass	5 (17.24%)	2 (8%)	0.301
Biliary + chemotherapy	3 (10.34%)	2 (8%)	
PTBD	1 (3.45%)	1 (4%)	
Metal stent + gastrojejunostomy	7 (24.14%)	0	
Cholecystostomy	0	1 (4%)	
Histopathological findings [n (%)]			
Adenocarcinoma	21 (72.41%)	17 (68%)	
Well-differentiated	6 (20.69%)	6 (24%)	0.696
Moderately differentiated	2 (6.90%)	0	
Poorly differentiated	0	2 (8%)	

Abbreviations: BMI= Body Mass Index, SGA= Subjective Global Assessment based on Canadian malnutrition task force (CMTF), SMV= Superior mesenteric vein, SMA= Superior mesenteric artery, CHA= Common hepatic artery, CA= Celiac artery, PTBD= Percutaneous transhepatic biliary drainage.

Bivariate analysis showed significant difference between unresectable and resectable groups for CA 19-9 ($p < 0.001$), Karnofsky score ($p < 0.001$), BMI ($p = 0.003$), SGA score ($p < 0.001$), serum albumin ($p = 0.030$), vascular involvement ($p < 0.001$), and metastasis ($p < 0.001$). These variables were then included in multivariate logistic regression analysis for bias control, except for vascular involvements and metastasis, as these parameters were used as a gold standard basis in assigning groups for subjects. Before multivariate analysis, numerical variables (albumin and Karnofsky score) were dichotomized using the area under the curve (AUC)-ROC curve to find the cutoff level. The result was 3.025 g/dL optimum level of albumin (sensitivity of 76% and specificity of 62.1%) and 85 values cut off for Karnofsky score (sensitivity of 80% and specificity of 69%).

Preoperative CA 19-9 levels and eligibility criteria for pancreatic head adenocarcinoma resection

This study recorded a 2698.40 ± 6843.33 U/mL mean level of CA 19-9 with some outlier data. The preoperative CA, 19-9 level of study subjects, are shown in Table 1, in which bivariate analysis using Mann-Whitney test showed significant difference for Ca-19-9 level between resectable and unresectable group ($p < 0.001$). We developed a ROC curve to find the AUC value and determine the CA 19-9 cutoff level with optimum sensitivity and specificity to predict resectable pancreatic head adenocarcinoma, as shown in Figure 1. The study found 0.784 AUC (SD = 0.065; CI (95%) = 0.656-0.912; $p < 0.001$). ROC curve showed the CA 19-9 cutoff level was 140.65 U/mL with the sensitivity of 82.76% (64.23%-84.15%) and specificity of 72.00% (50-61%-87.93%) as described in Table 2.

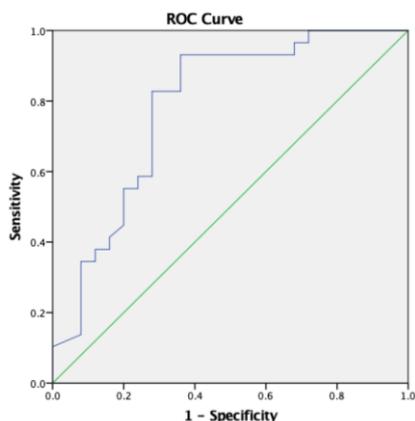


Figure 1. AUC-ROC curve for preoperative CA 19-9 level use in predicting resectable pancreatic head adenocarcinoma.

Table 2. Diagnostic Value of CA 19-9 level on 140.65 U/mL threshold as additional eligibility criteria for pancreatic head adenocarcinoma resection

Parameter	Value	CI (95%)
Sensitivity	82.76%	64.23%–94.15%
Specificity	72.00%	50.61%–87.93%
Positive predictive value	77.42%	64.15%–86.79%
Negative predictive value	78.26%	60.99%–89.23%
Positive likelihood ratio	2.96	1.54–5.66
Negative likelihood ratio	0.24	0.10–0.55

Further analysis found the difference between preoperative CA 19-9 between unresectable and resectable pancreatic head adenocarcinoma groups using the determined optimum CA 19-9 cut-off level. The Chi-square test showed a significant difference between the resectable and unresectable groups, as shown in Table 3.

Table 3. Proportion analysis of CA 19-9 between resectable and unresectable group

CA 19-9 (U/mL)	Group		OR (CI 95%)	P
	Unresectable n (%)	Resectable n (%)		
≥140.65	24 (82.76)	7 (14)	12.34	0.000*
<140.65	5 (17.24)	18 (76)	(3.4–45.3)	
Total	29	25		

*Chi-square test

Discussion

Subject Characteristics

This study found a statistically significant difference in Karnofsky score, BMI, SGA score, and albumin value. This finding may be related to the eligibility criteria for pancreatic head adenocarcinoma resection affected by malignancy stages, which would directly affect these factors. We also found elevated bilirubin levels in 86% of patients caused by CBD compression on the first stages of pancreatic head adenocarcinoma. Out of 25 resectable patients, only 10 (40%) could receive tumor resection procedure (Whipple procedure). This number may be related to the fast progression of adenocarcinoma and negative biliary drainage response, explaining why 60% of patients whose predicted as resectable through radiological modality were deemed inoperable before surgery.¹³

Diagnostic value of CA 19-9 to predict resectable pancreatic head adenocarcinoma

Prior studies had shown the potentials of preoperative CA 19-9 level as prognostic predictor pancreatic adenocarcinoma, as Dong et al.¹⁴ found >338.45 U/mL CA 19-9 level predicted a low one-year survival rate with a sensitivity of 60% and specificity of 66.7%. Following prognostic predictions, eligibility criteria for pancreatic head adenocarcinoma resection depend on adenocarcinoma cells infiltration to nearby tissue, in which a higher rate of infiltration would be reflected by a higher level of CA 19-9. This study demonstrated that CA 19-9 level could predict resectable pancreatic head adenocarcinoma accuracy up to the appropriate category.^{13,15}

This result was contradictory with Pandiaraja et al.⁴ study, which mentioned no relationship between CA 19-9 level and resectable pancreatic head adenocarcinoma; but Pandiaraja et al. used 37 U/mL CA 19-9 level as the optimum level, which was much lower than the optimum CA 19-9 level used in our study. Their study also failed to mention the obtained sensitivity and specificity from their analysis. Our study result was supported by other studies, such as Killic et al. [6] that found 256.4 U/mL CA 19-9 cut-off level with 82.4% sensitivity, 92.3% specificity, and 0.892 AUC. We believe the variation of sensitivity, specificity, and AUC value with our study was caused by the difference in patients' characteristics.

There haven't been many studies that evaluated CA 19-9 diagnostics values, as most studies focused on elevating the accuracy of CT scans. The use of CT scan is deemed easier and more efficient, but it should be noted that the availability of CT scan in Indonesia is scarce, so a more straightforward method using laboratory findings remains needed.

Multivariate analysis with logistic regressions

Different characteristics of patients may contribute to the interpretation of diagnostic modalities result, and there may be some confounding factors that work against the interpretation of the diagnostics modalities' sensitivity, specificity, and AUC value. We included various dependent variables other than CA 19-9 levels to test this possibility and found

Karnofsky score and albumin levels to affect resectable pancreatic head adenocarcinoma prediction. We tried to combine these factors with CA 19-9 levels and found elevated diagnostic value for CA 19-9 levels into an excellent category when combined with Karnofsky score and albumin levels.

Although the Karnofsky score is a clinical indicator and albumin has no specific link with the natural history of pancreatic head adenocarcinoma, both variables are commonly used to predict adequate physical condition before surgery and contributed to predicting operability. Thus, we believe these factors could be potential predictors of a patient's clinical prognosis post-surgery. No study has examined this possibility yet, and further study is needed to understand these variables' value as additional eligibility criteria for pancreatic head adenocarcinoma resection.¹⁵

Conclusion

There was a significant association between preoperative CA 19-9 and eligibility criteria for pancreatic head adenocarcinoma resection. There was also a significant difference in albumin levels and Karnofsky scores between the resectable and unresectable groups. Further studies with more samples from different healthcare settings are needed to evaluate CA 19-9 levels' prognostic values and possibly use combined indicators with albumin level and Karnofsky score.

Disclosure

Authors declare no conflict of interest

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