Correlation of Total Bilirubin with Serum CA 19-9 Levels of Pancreatic Cancer in H. Adam Malik Hospital Medan

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Abstract- **Introduction:** Pancreatic cancer is the seventh leading cause of death globally in developing countries. Through the process, elevated serum CA 19-9 levels have become a diagnostic tumour marker frequently used to detect pancreatic cancer. Studies have shown that adjusting CA19-9 levels to serum bilirubin levels can improve accuracy in differentiating between benign and malignant hepatopancreaticobilier disease.
Aim: We aimed to seek the correlation of bilirubin values with CA 19-9 levels in pancreatic cancer patients at H. Adam Malik General Hospital, Medan.
Methods: This is a descriptive-analytic study with a cross-sectional design with data collection carried out from July 2022 to November 2022, followed by processing and analysis of the data that has been collected. While the research sample was taken using the consecutive sampling method, determined with specific considerations, namely inclusion and exclusion criteria.
Results: The subject of this study averaged 62.59 + 4.28 years, the majority were male, as many as 159 people (78.3%), and the rest were female, as many as 44 people (21, 7%). Based on the staging, most research subjects were at stage III, as many as 78 people (38.4%), followed by subjects with stage II, as many as 50 people (24.6%); the rest were at stage IV, as many as 43 people (21.3%) and stage I as many as 32 people (15.7%). All study subjects found total bilirubin levels with an average value of 10.55 mg/dl with an SD of 2.75 mg/dl and CA19-9 levels with an average value of 145.28 U/ml an SD of 44.28. Then statistical analysis was carried out using the Spearman test and found a p-value <0.001 and a correlation coefficient of 0.971.
Conclusion: We found a significant relationship and strong correlation between CA 19-9 and total bilirubin in pancreatic cancer patients.

Index Terms- *Cancer, Pancreas Cancer, Ca 19-9, Serum Bilirubin*

I. INTRODUCTION

Pancreatic cancer is the seventh leading cause of death in developing countries and the third most common malignancy in the United States. Based on GLOBOCAN 2020 estimates, pancreatic cancer is the 12th most common cancer globally, with 495,773 new cases and causing 466,003 deaths (4.5% of all cancer deaths) in 2020. Incidence and mortality of pancreatic cancer worldwide are correlated with increasing age and sex of males compared to females (GLOBOCAN, 2020). The incidence of pancreatic cancer in Indonesia has increased over the past 40 years, with around 1000 cases diagnosed between 2015 and 2019. Although pancreatic cancer is not among Indonesia's ten most common cancers, it is the sixth and seventh leading cause of cancer death in men. -men and women in Indonesia (Ministry of Health, 2019). The cause of pancreatic cancer is complex and multifactorial, including smoking and a predominant family history. Pancreatic cancer is divided into two types, namely pancreatic adenocarcinoma, which most commonly (85% of cases) appears in the exocrine glands of the pancreas, and pancreatic neuroendocrine tumour (PanNET), which is less common around 1-2% and occurs in the endocrine tissue of the pancreas (Gillen et al., 2010).

Carbohydrate antigen 19-9 (CA 19-9) was first discovered by Koporowski et al. in colorectal cancer cells in 1979. After that discovery, elevated serum levels of CA 19-9 were associated with various disease processes, the most common of which are gastrointestinal malignancies, hepatobiliary cancer and pancreatic cancer. Carcinogenesis leads to abnormal synthesis and accumulation of these markers. CA 19-9 has become a diagnostic tumour marker frequently used to detect pancreatic cancer. Many

studies demonstrate its potential as a peri-operative prognostic marker for pancreatic cancer survival. CA19-9 remains the only clinically validated biomarker for pancreatic cancer. To improve the diagnostic accuracy of CA19-9, studies have shown that adjusting CA19-9 levels to serum bilirubin levels can improve accuracy in differentiating between benign and malignant hepatopancreaticobilier disease. The exact relationship between CA19-9 and bilirubin is not fully understood, but research evidence suggests that CA19-9 is increased in patients with hyperbilirubinemia, resulting in reduced specificity of CA19-9 in diagnosing hepatopancreaticobilier disease. (Liu, 2018).

In addition, examining the CA 19-9/bilirubin ratio has improved accuracy in characterizing biliary strictures. These comparisons show that bilirubin levels can be a helpful adjunct with other modalities. High bilirubin levels may prompt a more detailed evaluation (including as a tumour marker) to exclude underlying malignancy and may represent another factor in the multimodal assessment (Gracea et al., 2011). However, only a few studies have discussed the relationship between bilirubin levels and CA 19-9 levels in patients with pancreatic cancer, especially in North Sumatra. From this phenomenon, researchers were interested in examining the correlation of bilirubin values with CA 19-9 levels in pancreatic cancer patients at H. Adam Malik General Hospital, Medan.

II.   METHODS

The research is a descriptive-analytic study with a cross-sectional design to see the correlation of bilirubin levels with CA 19-9 levels in pancreatic cancer patients at H. Adam Malik General Hospital Medan with the approval of the USU FK Research Ethics Commission. Research and data collection will be carried out from July 2022 to November 2022, followed by processing and analysis of the data that has been collected. The population in this study were patients diagnosed with pancreatic cancer from January 2016 to December 2020 who were treated at Adam Malik Haji Center General Hospital Medan. While the research sample was taken using the consecutive sampling method, where the sample was determined with specific considerations, namely inclusion and exclusion criteria. The population of this study were all cancer patients at H. Adam Malik General Hospital. The sample of this study was all pancreatic cancer patients at H. Adam Malik General Hospital who met the inclusion criteria. The sampling technique used is total sampling. In determining the sample size in this retrospective cohort study, a sample of 79 patients was obtained.

The inclusion criteria for this study included inpatients or outpatients at H. Adam Malik General Hospital, patients with confirmed pancreatic cancer by histopathological examination and patients with bilirubin and CA 19-9 examination results. At the same time, the exclusion criteria were patients who had undergone cholecystectomy and patients with choledocholithiasis. This research begins by tracing medical record data to obtain demographic data consisting of age, sex, and stage of pancreatic cancer at H. Adam Malik General Hospital Medan and tracing medical record data to obtain data on the distribution of bilirubin levels, CA 19-9 levels. In pancreatic cancer patients at H. Adam Malik General Hospital Medan. Bilirubin levels are defined as total levels of bilirubin in the blood serum with average values: of 0.1 – 1.2 mg/dl measured using colourimetry with mg/dL units and a numerical scale, while CA levels 19-9 are defined as markers of pancreatic cancer found in blood serum with average values: 0 - 37 U/mL using a CMIA measuring instrument with units of U/mL and a numerical scale. Descriptive statistical analysis was used for demographic data. Statistical analysis on a continuous variable measuring scale is Pearson's correlation for normally distributed data and Spearman's correlation if the data is not normally distributed, which is used to test the correlation between variables regarding bilirubin levels and CA 19-9 levels in pancreatic cancer patients at H. Adam Malik General Hospital Medan.

III.   RESULTS

This study involved 203 research subjects who were patients diagnosed with pancreatic cancer from January 2016 to December 2020, treated at the Haji Adam Malik Medan General Hospital and met the exclusion and inclusion criteria. Data were collected using secondary data from medical records in the form of characteristic data (age, sex and staging), serum CA19-9 levels and serum total bilirubin levels. Then an analysis was performed using SPSS to assess the correlation of bilirubin values with CA19-9 levels in pancreatic cancer patients at H. Adam Malik General Hospital Medan. Pancreatic cancer patients who were the subjects of this study had an average age of 62.59 + 4.28 years, the majority were male, as many as 159 people (78.3%), and the rest were female, as many as 44 people (21.7%). %). Based on the staging, most research subjects were at stage III, as many as 78 people (38.4%), followed by subjects with stage II, as many as 50 people (24.6%); the rest were at stage IV, as many as 43 people (21.3%) and stage I as many as 32 people (15.7%) (Table 1).

Table 1. Demographic characteristics of study

Characteristics (N = 203)	Mean+SD
Age (Year), *Mean (SD)*	62,59 + 4,28 tahun
Gender, n (%)	
Male	159 (78,3%)
Female	44 (21,7%)
Stage, n (%)	
I	32 (15,7%)
II	50 (24,6%)
III	78 (38,4%)

Characteristics (N = 203)	Mean±SD
IV	43 (21,3%)

For the relationship between serum bilirubin levels and serum CA 1-9 levels, all study subjects found total bilirubin levels with an average value of 10.55 mg/dl with an SD of 2.75 mg/dl and found CA19-9 levels with an average value -average 145.28 U/ml with SD 44.28. Then statistical analysis was carried out using the Spearman test and found a p-value <0.001 and a correlation coefficient of 0.971 (Figure 1).
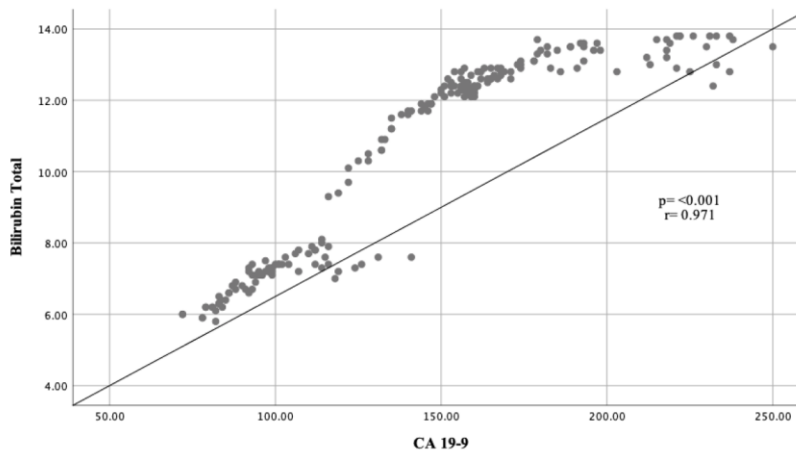

Figure 1. Relationship between Serum Bilirubin Levels and CA19-9 Serum Levels

IV.   DISCUSSION

Pancreatic carcinoma is one of the most common malignant tumours in the digestive system. Due to the high malignancy of the tumour itself, the condition is prone to local vascular invasion and distant metastases; the overall surgical resection rate is less than 20%. The five-year survival rate is less than 10%. According to the 2018 global cancer statistics, pancreatic cancer currently ranks 14th in the incidence of malignant tumours but 6th in mortality. Currently, radical resection is still the best treatment for pancreatic cancer. Therefore, it is essential to correctly assess the long-term prognosis of patients with pancreatic cancer before surgery to formulate a reasonable and practical treatment plan (Bray, Ferlay & Soerjomataram., 2018).

CA 19-9 is abnormally increased in patients with malignant tumours such as pancreatic cancer, cholangiocarcinoma and gallbladder cancer; a large number of studies have confirmed that CA19-9 is significantly associated with the diagnosis and prognosis of pancreatic cancer, as well as postoperative recurrence (Koprowski et al ., 2020). However, CA 19-9 is not specific to tumour cells and can also be synthesized in the normal human pancreas, bile duct, stomach, colon and other epithelial cells; therefore, low CA 19-9 can also be detected in normal human blood. However, when biliary obstruction occurs, CA 19-9 secreted by the bile duct epithelial cells cannot be excreted into the intestinal tract commonly, whereas CA 19-9 secreted by pancreatic epithelial cells can also flow back into the bile ducts.

Pancreatic cancer patients who were the subjects of this study had an average age of 62.59 + 4.28 years, the majority were male, as many as 159 people (78.3%), and the rest were female, as many as 44 people (21.7%). %). Based on the staging, most research subjects were at stage III, as many as 78 people (38.4%), followed by subjects with stage II, as many as 50 people (24.6%); the rest were at stage IV, as many as 43 people (21.3%) and stage I as many as 32 people (15.7%). This follows a study in Shanghai, China, in 2018, with the average age of pancreatic cancer patients being 61 years and the sex mostly being male, including those in the stage III group (Feng, 2018). These results align with research by Xu in 2021, which showed that the average age of pancreatic cancer patients was 63.4+10.1 years. A total of 339 patients with pancreatic head cancer, including 192 males and 147 females, with a male: female ratio of 1.3:1. Initial symptoms mainly included abdominal pain (n=146), jaundice (n=134), atypical gastrointestinal symptoms (n=19) and another 40 patients found during physical examination. Of all patients, 117 (34.5%) had a history of diabetes (Xu, 2021).

This study found total bilirubin levels with an average value of 10.55 mg/dl with an SD of 2.75 mg/dl and CA levels of 19-9 with an average value of 145.28 U/ml with an SD of 44.28. Then statistical analysis was carried out using the Spearman test and found a p-value <0.001 and a correlation coefficient of 0.971. Currently, CA 19-9 is still an important serological marker for the clinical diagnosis and prognosis of pancreatic cancer. O'Brien et al. demonstrated that at 95% specificity, CA 19-9 (>37 U/mL) had a sensitivity of 68% up to 1 year and 53% up to 2 years before diagnosis. Therefore, CA 19-9 is considered to be used in the early diagnosis of pancreatic cancer (O'Brien et al., 2020; Boeck et al., 2022).

Meanwhile, several studies have shown that the sensitivity of CA 19-9 in the diagnosis of pancreatic cancer is more than 80%. However, the accuracy of assessing benign or malignant disease is significantly reduced for patients with jaundice. It was suggested

that CA 19-9 should be adjusted according to the bilirubin index, but no feasible adjustment scheme was given. Previous studies have shown that the ratio of CA 19-9 to total bilirubin can be used to predict the recurrence of resectable pancreatic cancer, but enrolled patients also included 24.6% of patients who had cancer of the body and tail of the pancreas without jaundice, thus homogeneity of the studies. La Greca and other studies have shown that the ratio of CA 19-9 to total bilirubin can be used to differentiate between benign and malignant causes of obstructive jaundice, which can increase the specificity of the diagnosis (La Greca, 2012).

Bile duct obstruction caused by a benign process can cause bilirubin levels to rise. However, the bilirubin reaches much higher levels when the obstruction is due to a malignant disease. The exact relationship between CA 19-9 and bilirubin has yet to be fully understood. However, research evidence suggests that CA 19-9 increases in patients with hyperbilirubinemia, resulting in reduced specificity of CA 19-9 in diagnosing hepatopancreatic biliary disease. A pathophysiological explanation could be that the bile duct is a pathway for CA 19-9 excretion to the liver. Therefore, the obstruction causing hyperbilirubinemia may block bile flow, resulting in higher serum CA 19-9 levels. Based on this hypothesis, studies have shown that adjusting CA 19-9 to bilirubin by calculating the ratio of CA 19-9/total bilirubin can have a more substantial diagnostic value than CA 19-9 alone. However, the CA 19-9/bilirubin ratio where CA 19-9 is divided by bilirubin in the regression analysis has been questioned by statisticians, as it implies a linear relationship between these markers and does not accurately reflect the condition of patients, i.e. patients with CA levels of 19-9 Patients with high levels of bilirubin and high bilirubin can have the same ratio as patients with levels of CA 19-9 and low levels of bilirubin. Considering this, it is suggested to evaluate the ratio as the value of dividing CA 19-9 with the reciprocal of bilirubin (e.g., CA 19-9/(bilirubin−1)), based on the mathematical equation of Kronmal and collaborators, which takes this into account (Liu, 2020).

In a 2012 study in Barcelona, Spain, comparing patients with pancreatic tumours at stage I, patients with tumours at stage IV had statistically significantly lower direct and total bilirubin concentrations; it excels in both simple and multivariate models, adjusted for potential confounders. However, the relationship between bilirubin and stage is entirely attributable to the relationship between bilirubin, cholestatic syndrome, and early stage at presentation (Porta, 2012). This is consistent with the results obtained in this study, which show that bilirubin levels have a significant relationship with the stage of pancreatic cancer.

V. CONCLUSION

Pancreatic cancer patients who were the subjects of this study had an average age of 62.59 + 4.28 years; the majority were male, as many as 159 people (78.3%) and based on the staging of the study subjects, most were at stage III as many as 78 people (38.4%) and found a significant relationship and a strong correlation between CA 19-9 and total bilirubin in pancreatic cancer patients (p<0.001, r=0.971).

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