

The Differences of Pepsinogen I and *H. Pylori* Levels in Patients With Gastric Premalignant Lesion

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Abstract.

Background: Gastric cancer is the fifth most common cancer worldwide, precancerous lesions is triggered by *H. pylori* infection and any other factors. Recent reports confirmed that serum pepsinogens are a valuable biomarker gastric cancer even before the discovery of *H. pylori*.

Research Methods: This study is a cross-sectional study involving 80 confirmed patients with Gastric Premalignant Lesion at Adam Malik General Hospital, Permata Bunda General Hospital, Medan, on April-November 2018. These two variables is sought using the Mann Whitney test (normality test $P < 0,05$). *H. pylori* were diagnosed by positive result of examination of Carbon-14 urea breath test (C-UBT) or *Campylobacter-like organism* (CLO). Examination of Pepsinogen I measured by Abbott ARCHITECT Pepsinogen I Reagent Kit (Abbott Laboratories Inc., Chicago, IL, USA).

Result: Of the 60 participants who confirmed has *gastritis premalignant lesion* according to the inclusion criteria. From the table of characteristic descriptive, it was found that 48 patients were male (60%) and 32 patients were female (40%). From CLO and 14C-UBT, it was found 35 patients were *H. pylori-positive* (43,8%) and 45 patients were *H. pylori-negative* (56,3%). Mean age was 51.03 ± 10.97 years. Mean levels of Pepsinogen I was 44.28 ± 21.77 . From the second table, it was found that 35 (43,8%) patients with *H. pylori-positive* has 47.84 mean levels of Pepsinogen I, and 45 (56,3%) patients with *H. pylori-negative* has 34,79 mean levels of Pepsinogen I. The results of Mann Whitney's correlation analysis found a significant correlation between Pepsinogen (PG) I and *H. Pylori* in patients with *Gastric Premalignant Lesion* ($p < 0,05$).

Conclusion : It was found that there was a correlation between Pepsinogen (PG) I levels and *H. Pylori* in patients with *Gastric Premalignant Lesion* ($p < 0,05$).

Keywords : Gastric Cancer, Helicobacter Pylori, Pepsinogen, Gastric Premalignant Lesion

Abstrak.

Latar Belakang: Kanker lambung adalah kanker kelima tersering di dunia, lesi kanker premaligna dipicu oleh infeksi *H. pylori* dan faktor lainnya. Penelitian terbaru melaporkan

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bahwa serum pepsinogen ialah pertanda kanker lambung bahkan sebelum H. pylori terdiagnosa.

Metode dan Bahan: *Studi ini merupakan studi cross sectional atau studi potong lintang yang melibatkan 80 pasien dengan Gastric Premalignant Lesion di Rumah Sakit Umum Pusat H. Adam Malik dan Rumah Sakit Umum Permata Bunda, Medan pada April – November 2018. Diagnosis H. pylori ditegakkan berdasarkan salah satu hasil positif dari pemeriksaan Carbon-14 urea breath test (C-UBT) atau pemeriksaan Campylobacter-like organism (CLO). Pemeriksaan kadar Pepsinogen I dilakukan menggunakan Abbott ARCHITECT Pepsinogen I Reagent Kit (Abbott Laboratories Inc., Chicago, IL, USA). Kedua variabel ini diolah menggunakan uji Mann Whitney (Uji Normalitas $P < 0,05$).*

Hasil : *Dari 80 orang penderita dengan lesi premaligna lambung sesuai dengan kriteria inklusi. Dari tabel distribusi karakteristik ditemukan, pasien jenis kelamin laki-laki sebanyak 48 orang (60%) dan perempuan sebanyak 32 orang (40%). Berdasarkan pemeriksaan CLO atau 14C-UBT, didapati hasil positif H. pylori pada 35 orang (43,8%) dan negative H. pylori pada 45 orang (56,3%). Nilai rata-rata umur adalah 51.03 ± 10.97 tahun dengan nilai rata-rata kadar Pepsinogen I sebesar 44.28 ± 21.77 . Dari tabel perbedaan pepsinogen dan H. pylori, didapatkan bahwa kadar Pepsinogen I pada 35 (43,8%) pasien positif H. pylori adalah rata-rata 47,84, dan kadar Pepsinogen I pada 45 (56,3%) pasien negatif H. pylori adalah rata-rata 34,79. Dari uji analisis komparatif Mann Whitney, disimpulkan adanya perbedaan yang signifikan antara kadar Pepsinogen (PG) I dan H. pylori pada pasien dengan Gastric Premalignant Lesion ($p < 0,05$).*

Kesimpulan : *Ditemukan adanya korelasi kadar Pepsinogen (PG) I dan H. pylori pada pasien dengan Gastric Premalignant Lesion ($p < 0,05$).*

Kata Kunci: *Kanker lambung, Helicobacter Pylori, Pepsinogen, Gastric Premalignant Lesion*

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1 Introduction

Gastrointestinal cancer mortality rate is still high enough, despite there are already advance medical technologies and good medications for gastrointestinal disease.¹ From the studies in gastrointestinal cancer, early detection can reduce morbidity and improve the survival of patients.¹ Gastric cancer is the fifth most common cancer worldwide and third highest cause of cancer-related death. In worldwide 2012, 950000 individuals were diagnosed with the disease and 723000 died. High incidence areas are Eastern Asia, particularly China, Japan and South Korea, Eastern Europe, Central and South America. Low incidence areas are Australia and New Zealand, North America, Western Europe, South Central Asia and most parts of Africa.²

Gastrointestinal cancers arise through a cascade of precursor that is already known about inflammatory – ranging from metaplasia-dysplasia-carcinoma sequence, so it is always via the stages of precancerous lesions.³ Precancerous lesions can be defined as a change or a non-cancerous lesions that can become cancerous over time. Precancerous lesion is a common condition associated with increased risk to turn into cancer. If left untreated the condition will turn into cancer.⁴ Precancerous lesions can be found on the entire upper and lower gastrointestinal tract. Precancerous lesions of the upper digestive tract that can be found are Barrett's esophagus, chronic gastritis with or without *Helicobacter pylori* infection, atrophic gastritis, intestinal

metaplasia of the gastric mucosa, epithelial dysplasia, and adenoma polyp.^{3,5} In the gastric, intestinal-type metaplasia is the most common form of metaplasia, it can be a precursor to gastric cancer, including precancerous lesions because it is associated with the development of adenomas and well-differentiated adenocarcinomas. However, intestinal metaplasia is not always progressive to gastric cancer. Gastric carcinogenesis is often the result of *H. pylori* infection.⁶

Helicobacter pylori has a unique capacity to persistently colonize the extremely acidic environment of the stomach and cause progressive gastric mucosal inflammation. Long-term infection induces a multistep histological cascade, from chronic non-atrophic gastritis that progresses to chronic atrophic gastritis, intestinal metaplasia, and adenocarcinoma.⁷ Recent reports confirmed that serum pepsinogens are a valuable biomarker of the gastric mucosal status, including inflammation, atrophic gastritis, and gastric cancer, even before the discovery of *H. pylori*.^{7,8} Although the most part of pepsinogens are secreted by the gastric cells and, in low levels, are permeated into serum. Low serum pepsinogen levels can also predict this phenotype and, in such patients, *Helicobacter pylori* serology may be useful for further detection of high risk individuals. Pepsinogen I and pepsinogen II, the two main types of pepsinogens are produced in different regions of the stomach. Serum pepsinogen I, which is secreted purely on the fundus, decreases progressively, therefore, pepsinogen I/II ratios serve as a gastric mucosal biomarker and can be applied to gastric cancer screening.⁷

2 Research Methods

Subject Selection: 80 confirmed patients with Gastric Premalignant Lesion at Adam Malik General Hospital, Permata Bunda General Hospital, Medan, on April-November 2018 were involved in this study. Inclusion criteria were patients with diagnosed *gastritis premalignant lesion* based on histopathology after procedure, male and female > 18 years old, cooperative and willing to participate in this study. Exclusion criteria included patients with malignancy, history of gastric surgery before and pregnancy. Written informed consent was obtained from all participants and the study protocol was approved by the clinical research ethics committee of Universitas Sumatera Utara.

Study Procedure: The diagnosis of *H. pylori* is based on one positive result from the Carbon-14 urea breath test (C-UBT) or the Campylobacter-like organism (CLO) test, also known as the Rapid Urease Test. Before being examined by C-UBT, the patient is asked to fast for a minimum of 6 hours. Then the patient drank 37 kBq (1 μ Ci) C urea / Citric acid which was composed in capsules dissolved in 25ml of mineral water. The breath samples were collected on HeliProbe Breath Cards (Noster system) after 10 minutes of taking C urea. The patient does the expiration on the HBC card until the indicator changes color from orange to yellow. The sample was then examined using a Heli probe analyzer for 250 seconds with the results stated as the amount per minute (counts per minute - cpm). If the result is <25 cpm, then it is declared HeliProbe 0

(uninfected). If the result is 25-50 cpm, it is declared as Heliprobe 1 (equivocal) and if the result is > 50 cm it is declared as Heliprobe 2 (infected). CLO examination or Rapid Urease Test is a test used to diagnose *H.pylori* infection. The results of the examination are read within 24 hours. A negative result is obtained if the test results show a yellow color, while a positive result is stated if the yellow color turns pink within 24 hours of incubation at room temperature. Pepsinogen I levels were examined using the Abbott ARCHITECT Pepsinogen I Reagent Kit (Abbott Laboratories Inc., Chicago, IL, USA).

Statistical Methods: This study is a cross-sectional study which was held on April-November 2018 at Adam Malik General Hospital, Permata Bunda General Hospital, Medan.

Statistical Analysis : After examining the Pepsinogen I levels and *H. pylori* status has diagnosed, the data will be tabulated and analyzed using SPSS through the Kolmogorov Smirnov Normality test and the result was $p = 0.001$ ($p < 0.05$) so it can be concluded that the data are not normally distributed (non-parametric). Therefore, the data were further analyzed using the Mann-Whitney comparative test.

3 Result

The univariate research method was used to observe the distribution of the characteristics of the 80 research samples.

Table 1 Distribution of Samples Characteristics

Variable	N = 80
Age	51.03 ± 10.97
Gender	
Male	48 (60%)
Female	32 (40%)
Ethnic	
Bataknese	51 (63.7%)
Jawanese	23 (28.7%)
Aceh	6 (7.5%)
<i>H. Pylori</i>	
Positive	35 (43.8%)
Negative	45 (56.3%)
Pepsinogen I Level	44.28 ± 21.77

Based on table 1, we found that 48 (60%) samples were male and 32 samples were female (40%). According to CLO or ¹⁴C-UBT, we found as much as 35 (43,8%) samples were *H. pylori*-positive and 45 (56,3%) were *H. pylori*-negative. Mean age was 51.03 ± 10.97 years. Mean levels of Pepsinogen I was 44.28 ± 21.77.

Table 2 Differences between PG I level and *H. Pylori* in Gastric Premalignant Lesion Patients.

	<i>H. pylori</i>	N = 80	Mean	P value
PG I Level	Positive	35 (43.8%)	47.84	0,013
	Negative	45 (56.3%)	34.79	

From the second table, it was found that 35 (43,8%) patients with *H. pylori*-positive has 47.84 mean levels of Pepsinogen I, and 45 (56,3%) patients with *H. pylori*-negative has 34,79 mean levels of Pepsinogen I. The results of Mann Whitney's correlation analysis found a significant correlation between Pepsinogen (PG) I and *H. Pylori* in patients with Gastric Premalignant Lesion ($p < 0,05$).

4 Discussion

From 80 samples, most patients (60%) were male and the mean age of samples was 51,03 years old. We found that most patients in this research were Batakese (63,7%). Siregar et al (2020) found that 54,2% patients with gastric premalignant lesion were male and 63,7% were Batakese. In this study, there were a significant associations between Batakese and gastric premalignant lesion.⁹ In the other hand, den Hoed et al (2011) reported there were no significant associations between gender and gastric premalignant lesion, but they found that age was risk factor for this case.¹⁰ The mean age of samples in our study were lower than den Hoed et al (2011). In their study, most of gastric premalignant lesion patients was over 60 years old.¹⁰ Our other study found that most of gastric premalignant lesion patients was over 49 years old, however the significant associations between age and gastric premalignant lesion was not found.⁹

Helicobacter pylori has an ability to colonize in the extremely acidic environment of the stomach and cause progressive gastric mucosal inflammation.⁷ Chronic inflammation that caused by *H. Pylori* contribute in gastric cancer pathogenesis, but only a small percentage of individuals will develop to pre-neoplastic cascade.^{11,12} Oxidative stress on the gastric mucosa due to *H. pylori* infection is an important contributing factor to gastric carcinogenesis. Previous study stated that this infection is correlated with an increase of gastric mucosa destruction.^{13,14}

In our study, 43,8% patients were *H. pylori*-positive and 56,2% were negative through CLO or 14C-UBT examination. This result is different compared to Cho et al (2017) where 76% seropositive *H. pylori* was found in patients with gastric neoplasm and showed a significant differences compared to subjects without neoplasm.¹⁵ Tepes et al (2017) was found similar result with Cho et al (2017). In their study, there were 76% patients with gastric premalignant lesion have seropositive *H. pylori* and it significantly increase according to age. *H.pylori*-negative can occur if the pre-neoplastic changes were diffused, so that *H. pylori* no longer found in gaster.^{16,17} This found are also unabele to prove that the patient has never had *H. pylori* infection before. In addition, although CLO has high sensitivity (85-97%) and specificity (92%), it also has the

possibility of false negative results in gastric atrophy or intestinal metaplasia due to uneven distribution of bacteria in the mucosa.^{18,19}

We found that pepsinogen I level in patients with gastric premalignant lesion was 44,28. In *H. pylori*-positive patients, the PG I level was 47,84. Meanwhile, in *H. pylori*-negative patients, PG I levels were lower (34,79). As previously mentioned, *H. pylori* is capable of causing persistent active chronic inflammation. This condition will lead to atrophy and destruction of the gastric glands. As the result of destruction, chief cells are replaced by pyloric glands. It will affect the production of pepsinogen I which should be secreted by fundus glands, so the phenomenon that occurs is decrease of pepsinogen I level and PG I/II ratio.²⁰ Several studies reported that pepsinogen serum level was significantly related to widespread chronic gastritis and this test has become a screening program for gastric cancer in Japan. There are many reference values used, but the widely accepted predictors for gastric cancer are PG I ≤ 70 ng / mL and PG I / II ≤ 3 .^{21,22}

There were a significant differences of PG I level in *H. pylori*-positive compared to *H. pylori*-negative. The result of this study are different from Kikuchi et al (2000) who found that PG I serum levels were lower in *H. pylori*-positive.²³ Bornschein et al (2012) reported that PG I, PG II, G17 levels did not differ between *H. pylori*-positive and -negative groups. Patients with gastric atrophy showed lower PG I level than patients without atrophy ($p < 0,001$). All the serum parameters (PG I, PG II, G17 levels) did not show a significant differences between proximal and distal carcinoma.²⁴

Another factor that related to PG I levels were reported by Cha and Jang (2020). In their study, there were found that older patient and have atrophy changes in the proximal location of gaster showed lower PG I level and PG I/II ratio, but they have more severe atrophy in endoscopy examination.²⁵ The limitation of our study is we do not perform endoscopy in our subjects to observe the extent of atrophy. Thus, we were unable to determine the significant differences of pepsinogen I levels in *H. pylori*-positive and -negative groups was purely related to *H. pylori* infection or influenced by other factors, such as an extent of atrophy.

5 Conclusion

It was found that there was a correlation between Pepsinogen (PG) I levels and *H. Pylori* in patients with *Gastric Premalignant Lesion* ($p < 0,05$). However, we suggest that it be investigated further in the next research regarding the things that can influence this difference in PG I levels apart from *H. pylori* infection.

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