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Risk Factors of Gastric Premalignant Lesion in Gastritis Patients

(Faktor Risiko Lesi Gastrik Premalignan pada Pesakit Gastritis)

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ABSTRACT

Gastric cancer is the second leading cause of cancer-related mortality and the fourth most common cancer globally. Gastric premalignant lesions are well known risk factors for the development of gastric cancer. The purpose of this study was to investigate the risk factors of gastric premalignant lesion. This cross-sectional study observed gastritis patients at Adam Malik General Hospital, Permata Bunda General Hospital, Universitas Sumatera Utara Hospital, all located in Medan, Indonesia. A total of 120 gastritis patients were included in this study. Patients were interviewed with a questionnaire to obtain demographic data, alcohol intake, smoking status, high salt diet and NSAID use. Diagnosis of Helicobacter pylori *infection was made using positive results of the carbon-14 urea breath test (^{14}C-UBT), rapid urease test, and/or immunohistochemistry. Endoscopy and biopsy were conducted to diagnose gastric premalignant lesion. Gastric premalignant lesion diagnosis was made when one or more of the following were present: Chronic atrophic gastritis, intestinal metaplasia, or dysplasia. Data were analysed using SPSS version 22. There were 35/120 (29.2%) of gastritis patients having gastric premalignant lesion. Multivariate analysis has shown that* H. pylori *infection, patients with family history of gastric cancer, alcohol consumption and Batak ethnic have increased risk to develop gastric premalignant lesion (*$p<0.05$*). All these results implied that risk factors of gastric premalignant lesion were* H. pylori *infection, family history of gastric cancer, alcohol intake and Batak ethnic.*

Keywords: Gastric cancer; gastric premalignant lesion; Helicobacter pylori*; risk factors*

ABSTRAK

Kanser gastrik merupakan penyebab kedua terbesar dalam kejadian kematian berkaitan dengan kanser dan berada di tempat keempat dalam kejadian kanser yang paling sering terjadi di seluruh dunia. Faktor risiko yang terkenal dalam perkembangan kanser gastrik adalah lesi gastrik premalignan. Objektif penyelidikan ini adalah untuk mengkaji faktor risiko kejadian lesi gastrik premalignan. Kajian keratan rentas ini dilakukan pada pesakit gastritis di hospital yang berlokasi di Medan, Indonesia seperti Hospital Umum Adam Malik, Hospital Umum Permata Bunda dan Hospital Universiti Sumatera Utara. Jumlah pesakit gastriris yang terlibat dalam penyelidikan ini adalah seramai 120 orang. Pesakit ditemu duga dengan soal selidik yang merangkumi pertanyaan mengenai data demografi, pengunaan alkohol, status penghisapan rokok, diet yang mengandungi garam tinggi serta penggunaan ubat NSAID. Diagnosis pada infeksi Helicobacter pylori *ditentukan daripada hasil positif pada ujian karbon-14 pernafasan urea (^{14}C-UBT), ujian pantas urease dan/atau immunohistokimia. Endoskopi dan biopsi dijalankan untuk pendiagnosisan lesi gastrik premalignan. Diagnosis lesi gastrik premalignan dilakukan sekiranya salah satu daripada lesi ini ditemui: Gastritis atrofik kronik dan/atau metaplasia atau displasia usus. Data dianalisis dengan menggunakan SPSS versi 22. 35 daripada 120 (29.2%) pesakit gastritis mempunyai lesi gastrik premalignan. Analisis secara multivariat menunjukkan bahawa infeksi* H. pylori*, pesakit dengan sejarah keluarga kanser gastrik, penggunaan alkohol serta etnik Batak didapati meningkatkan risiko perkembangan lesi gastrik premalignan (*$p<0.05$*). Kesimpulannya, keputusan kajian menunjukkan bahawa faktor risiko terjadinya lesi gastrik premalignan adalah infeksi* H. pylori*, pesakit dengan sejarah keluarga kanser gastrik, penggunaan alkohol dan etnik Batak.*

Kata kunci: Faktor risiko; Helicobacter pylori*; kanser gastrik; lesi gastrik premalignan*

INTRODUCTION

Gastric cancer is the second leading cause of cancer-related mortality and the fourth most common cancer globally. Significantly more gastric cancer cases were noted in less developed regions compared to more developed regions (Ang & Fock 2014; Ferlay et al. 2008; Karim-Kos et al. 2008). Although the incidence of gastric cancer is declining, it still remains a major health problem and a common cause of cancer mortality worldwide (Rahman et al. 2014; Zali et al. 2011).

Gastric carcinogenesis is a multistep and multifactorial process (Hu et al. 2012; Ishaq & Nunn 2015). Risk factors of gastric cancer are *Helicobacter pylori* infection, salt intake, smoking, alcohol, family history of gastric cancer and presence of gastric premalignant lesion such as atrophic gastritis, intestinal metaplasia and dysplasia.

Gastric premalignant lesions are well known risk factors for the development of gastric cancer (Almouradi et al. 2013; Crew et al. 2016; De Vries et al. 2008; Lage et al. 2016; Park & Kim 2015; Song et al. 2015; Yeh et al. 2009; Zhang et al. 2017; Zullo et al. 2012).

However, since symptoms are most frequently absent in patients with gastric premalignant lesion, epidemiology of these lesion is largely unknown, especially in regions with a relatively low incidence of gastric cancer (Cheung 2017; Weck & Brenner 2006). Identification and surveillance of patients with gastric premalignant lesion may lead to prevention of gastric cancer. Detection of gastric premalignant lesions is critical because they predict risk of malignant transformation, may assist in timely diagnosis of gastric cancer and consequently a better prognosis (De Vries et al. 2007; Yashima et al. 2010).

Therefore, it is very important to investigate the risk factors of gastric premalignant lesion. By eliminating these risk factors, the incidence of gastric premalignant lesion would be lowered, so that gastric cancer eventually may be decreased.

Materials and Methods

Patient selection

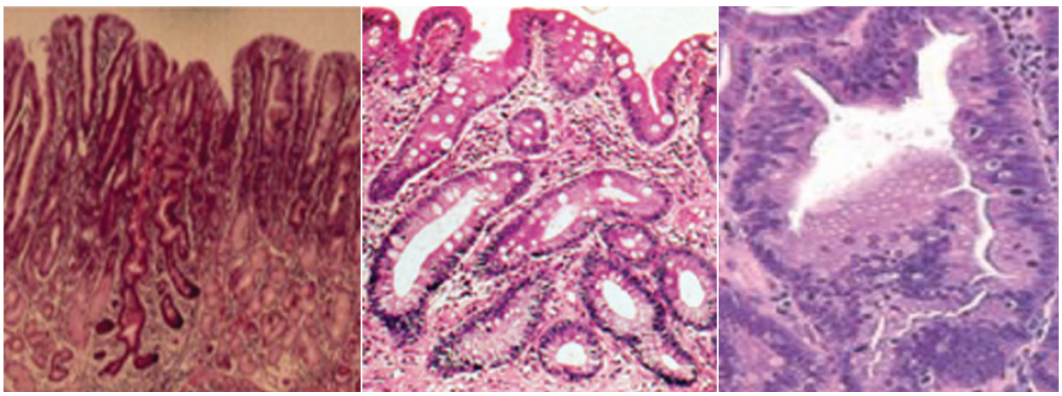
This study was a cross-sectional study on 120 consecutive gastritis patients that were admitted to Endoscopy Units at Adam Malik General Hospital, Permata Bunda General Hospital, Universitas Sumatera Utara Hospital, Medan, Indonesia between October and December 2017. Inclusion criteria were patients diagnosed with gastritis from histopathology, age > 18 years, cooperative and willing to participate. Exclusion criteria included patients who have received *H. pylori* eradication therapy in the last 6 months or are currently on antibiotic therapy commonly used in eradication, pregnancy, suspected gastric malignancy, prior gastric surgery, concomitant use of proton pump inhibitors or H2 antagonists receptor. Written informed consent was obtained from all participants and the study protocol was approved by the clinical research ethics committee of Universitas Sumatera Utara. All participants were interviewed on their medical and family histories, followed by a brief physical examination. A structured questionnaire elicited informative on demographic data, alcohol intake, smoking status, high salt diet and NSAID use.

Diagnosis of gastric premalignant lesion

Tissue biopsy was performed within the greater and lesser curvature of the distal antrum, lesser curvature at incisura angularis, anterior and posterior wall of proximal corpus. Additional biopsies were also done in suspicious regions that were not mentioned previously. Microscopic observations were performed to diagnose gastric premalignant lesion (chronic atrophic gastritis, intestinal metaplasia and dysplasia) (Figure 1). One or a combination of these three disorders is called a gastric premalignant lesion. Histopathologic examination was done by 2 Pathologists at Universitas Sumatera Utara blindly. If there were differences in the results of the examination of both experts, then a third Pathologist to perform histopathological examination was required.

H. pylori detection

Diagnosis of *H. pylori* based on the positive results of carbon-14 urea breath test (^{14}C-UBT), rapid urease test and/or immunohistochemistry. Prior to ^{14}C-UBT, patients had fasting for at least 6 h, usually overnight. Then, patients swallowed 37 kBq (1 μCi) of encapsulated ^{14}C urea/citric acid composition with 25 mL water. Breath samples of patients were collected into Heliprobe Breath Cards (Noster system) within 10 min after administration of the ^{14}C urea. Then patients exhaled onto the breath card until its colour indicator changed from orange to yellow. The breath samples were measured using the Heliprobe analyzer in



1A 1B 1C

FIGURE 1. Gastric premalignant lesions (A) Atrophy gastritis characterized by loss of gastric glands. (B) Intestinal metaplasia: the gastric epithelium is replaced by intestinal type of epithelium. The intestinal epithelium has goblet cells. (C) Dysplasia: cellular atypia, abnormal differentiation, and dysorganized architecture

the period of 250 s. The results were expressed as counts per minute (cpm) with the reference values as follow. If the counts return to the value of < 25 cpm, then the result were defined as Heliprobe 0 (not infected). If the counts were between 25 and 50 cpm, this is defined as Heliprobe 1 (equivocal) and counts > 25 cpm is defined as Heliprobe 2 (infected) (Den Hoed et al. 2011).

The rapid urease test (Pronto Dry®, France) was used to establish the diagnosis of *H. pylori* infection. The results were read within 24 h. The yellow colour indicated a negative result. A positive result was reported if the colour changed from amber to pink-red within 24 h of incubation at room temperature (Rojborwonwitaya et al. 2005).

Immunohistochemical (IHC) staining for evaluation of *H. pylori* status carried-out with procedure as follows. Tissue sections were deparaffinized, rehydrated and pretreated with Proteinase K for 8 min and incubated with ChemMate Peroxidase Blocking Solution in room temperature for 10 min. The slides were subsequently incubated with the polyclonal rabbit anti- *H. pylori* primary antibody (B0471: Dako Corporation, Glostrup, Denmark) with a dilution of 1:50 was conducted at room temperature for 1 h. After samples had been washed 3 times with phosphate-buffered saline, the Dako EnVision Dual Link System–HRP (K4065: Dako Corporation) was applied for 30 min. Finally, sections were incubated in diaminobenzidine for 10 min, followed by hematoxylin counterstaining and mounting. *H. pylori* infected gastric mucosa from chronic gastritis patients served as positive controls. Negative controls were obtained by replacing the primary antibody with phosphate-buffered saline. *H. pylori* infection in the tissue sections was confirmed when short, curved or spiral bacilli resting on the epithelial surface, in the mucus layer, or deep in the gastric pits can be observed by light microscopy (Figure 2).

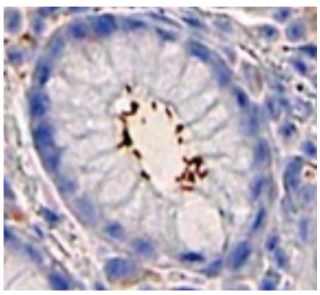


FIGURE 2. *H. pylori* in the gaster tissues by immunohistochemistry (IHC)

STATISTICAL METHODS

Data analysis was performed using the SPSS 22 version (SPSS Inc., Chicago) with a 95% confidence interval. Analysis was performed using chi square test and binary logistic regression with significance $p<0.05$.

RESULTS AND DISCUSSION

CHARACTERISTICS OF SUBJECTS

Amongst the 120 patients, 54.2% were male with a median age of 49 years. The largest ethnic group was Batak (55.8%). There were 61.7% of patients infected with *H. pylori*. About 13.3% of patients consumed alcohol, 45% smoked, 15% of patients with high salt intake and 11.7% with concomitant use of NSAID.

PREVALENCE OF GASTRIC PREMALIGNANT LESION

A total of 29.2% of gastritis patients had chronic atrophic gastritis, 25.8% intestinal metaplasia and 3.3% dysplasia. Most patients had overlapping lesions. One or a combination of these three disorders is called a gastric premalignant lesion. There were 29.2% (35 patients) of gastritis patients with gastric premalignant lesion (Table 1). These results vary greatly compared to previous studies. Den Hoed et al. (2011) in the Netherlands, De Vries et al. (2007) in the Netherlands, Roman et al. (2016) in St Petersburg found the prevalence of gastric premalignant lesion were 9.3%, 14%, 10.8%, respectively. While Haziri et al. (2010) in Kosova reported a high prevalence of gastric premalignant lesion in *H. pylori* infection, atrophic gastritis in 66%, intestinal metaplasia in 71.7%, dysplasia in 71.4%. Bedoya et al. (2012) in Colombia reported a prevalence of chronic atrophic gastritis in *H. pylori* infection of 38.5%, 24.5% intestinal metaplasia and 1.6% dysplasia. Maran et al. (2013) reported that ethnic differences influenced the risk of gastric premalignant lesion, due to genetic variation. In addition, rates of *H. pylori* infection and diets such as smoked and salted foods, meat, alcohol consumption vary between countries.

TABLE 1. Prevalence of gastric premalignant lesion

Diagnosis	Present (%)
Gastritis with gastric premalignant lesion (one or combination of chronic atrophic gastritis, intestinal metaplasia, and dysplasia)	35 (29.2)
Gastritis without gastric premalignant lesion	85 (70.8)

ASSOCIATION BETWEEN DEMOGRAPHIC CHARACTERISTICS, OVERWEIGHT, LIFESTYLE, FAMILY HISTORY OF GASTRIC CANCER, *H. PYLORI* INFECTION WITH GASTRIC PREMALIGNANT LESION

There were significant associations between age, Batak ethnic, alcohol intake, *H. pylori* infection, family history of gastric cancer with gastric premalignant lesion (Table 2). From results of multivariate analysis, *H. pylori* infection was most associated with gastric premalignant lesion, followed by family history of gastric cancer, alcohol intake and Batak ethnic (Table 3).

TABLE 2. Association between demographic characteristics, overweight, lifestyle, family history of gastric cancer, *H. pylori* infection with gastric premalignant lesion

Variable	Gastric premalignant lesion		Total	p	PR (95% CI)
	Yes	No			
Gender					
Male	23 (35.4%)	42 (64.6%)	65 (100%)	0.103	1.62 (0.89-2.95)
Female	12 (21.8%)	43 (78.2%)	55 (100%)		
Age					
≥49years	24 (38.1%)	39 (61.9%)	63 (100%)	0.024*	1.97 (1.07-3.66)
<49 years	11 (19.3%)	46 (80.7%)	57 (100%)		
Education					
Low level	9 (45%)	11 (55%)	20 (100%)	0.088	1.73 (0.96-3.11)
High level	26 (26%)	74 (74%)	100 (100%)		
Ethnic					
Batak	25 (37.3%)	42 (62.7%)	67 (100%)	0.027*	1.98 (1.04-3.75)
Non-Batak	10 (18.9%)	43 (81.1%)	53 (100%)		
Overweight					
Yes	12 (22.2%)	42(77.8%)	54 (100%)	0.130	0.64 (0.35-1.16)
No	23 (34.8%)	43 (65.2%)	66 (100%)		
Alcohol intake					
Present	9 (56.3%)	7 (43.8%)	16 (100%)	0.017*	2.25 (1.3-3.88)
Absent	26 (25%)	78 (75%)	104 (100%)		
Smoking status					
Present	11 (20.4%)	43 (79.6%)	54 (100%)	0.055	0.56 (0.3-1.04)
Absent	24 (36.4%)	42 (63.6%)	66 (100%)		
H. pylori					
Positive	31 (41.9%)	43 (58.1%)	74 (100%)	<0.001*	4.82 (1.82-12.76)
Negative	4 (8.7%)	42 (91.3%)	46 (100%)		
Family history of gastric cancer					
Present	5 (83.3%)	1 (16.7%)	6 (100%)	0.008*	3.17 (1.98-5.08)
Absent	30 (26.3%)	84 (73.7%)	114 (100%)		
High salt diet					
Present	5 (27.8%)	13 (72.2%)	18 (100%)	0.888	0.94 (0.42-2.11)
Absent	30 (29.4%)	72 (70.6%)	102 (100%)		
NSAID use					
Present	7 (50%)	7 (50%)	14 (100%)	0.113	1.89 (1.02-3.49)
Absent	28 (26.4%)	78 (73.6%)	106 (100%)		

*$p<0.05$

TABLE 3. Multivariate analysis of factors associated with gastric premalignant lesion

Variable	p	PR (95% CI)
H. pylori infection	0.003*	4.63 (1.81-11.73)
Family history of gastric cancer	0.016*	3.02 (1.81-4.97)
Alcohol intake	0.034*	1.94 (1.27-3.75)
Batak ethnic	0.042*	1.69 (1.02-3.49)
Age ≥ 49 years	0.440	1.45 (0.68-2.31)

*$p<0.05$

Although from previous study, males more susceptible to have gastric cancer than female, probably due to smoking and alcohol consumption (Karimi et al. 2014), however, in this study, no significant associations were found between gender and gastric premalignant lesion ($p>0.05$). This result is supported by previous studies. Den Hoed et al. (2011) in the Netherlands, Benberin et al. (2013) in Kazakhstan and Mansour-Ghanaei et al. (2013) in Iran have found no significant association between gender and gastric premalignant lesion. Liu et al. (2010) and Malik et al. (2017) reported that more males had gastric premalignant lesion than females, but did not

differ significantly. This study found that all patients with dysplasia were males. Although there was no difference in the percentage of male and female in the overall gastric premalignant lesion, none of the females experienced dysplasia, presumably hormonal factors play a role here. Previous studies found that men are at higher risk of developing gastric cancers. Zhou et al. (2013) reported that estrogen hormones are protective against gastric cancer. Overexpression of estrogen receptor can decrease motility and invasion of cancer cells by inhibiting cell growth and malignant progression.

A multicenter prospective study in Korea reported that age> 61 years was a risk factor for atrophic gastritis and intestinal metaplasia (Kim et al. 2008). Patients with gastric premalignant lesion were associated with older age than control group (mean age 60 years vs. 52.5 years, $p<0.01$) (Den Hoed et al. 2011). Benberin et al. (2013) also reported that prevalence of gastric premalignant lesion increased with age. This condition was rare in individuals under the age of 40. While Malik et al. (2017) reported aging was not a risk factor for gastric premalignant lesion. The result of bivariate analysis of this study found a significant association between age and gastric premalignant lesion, but the association became insignificant through multivariate analysis. This suggests that age factor is not a significant risk factor for the occurrence of gastric premalignant lesion.

The major ethnic group in this study was Batak (55.8%), since they inhabit most of North Sumatera region (Ambarsari et al. 2012). Batak was one of the ethnic in Indonesia with high rate of *H. pylori* infection (Syam et al. 2015). Batak ethnic has a habit of consuming alcohol both in traditional ceremony and daily life (Gaol & Husin 2013). There was a significant association between ethnicity and gastric premaligant lesion from bivariate analysis and remained significant through multivariate analysis. The Batak ethnic increased risk of 1.69 times to experience gastric premalignant lesion ($p=0.042$). However, further study is needed to evaluate the high prevalence of gastric premalignant lesion in Batak ethnic. Background of genetic factors, nutritional factors or lifestyle, immune response to *H. pylori* infection may be considered.

The prevalence of *H. pylori* varies greatly between geographic areas related to personal and environmental hygiene. India, China, Turkey, the Dominican Republic and Brazil reported the prevalence of *H. pylori* infection were 65.9%, 44.92%, 65% 58.9%, 30.93%, respectively (Adlekha et al. 2013; Bilman et al. 2016; Li et al. 2016; Shiota et al. 2014; Trindade et al. 2017). There was a significant association between *H. pylori* infection and gastric premalignant lesion ($p=0.003$), where patients with *H. pylori* infection had a 4.63-fold risk of gastric premalignant lesion. Previous studies in Korea by Joo et al. (2013) and Kim et al. (2008) reported *H. pylori* is a major risk factor for both atrophic and intestinal metaplasia. *H. pylori* is a Type 1 carcinogen according to International Agency for Research on Cancer (IARC). *H. pylori* CagA (+) as well as interactions between peptidoglycans with host defense molecules will induce increased proinflammatory cytokines through NF-κβ activation. IL-8 which is one of proinflammatory cytokines is a chemoattractant for neutrophils and monocytes (Szoke 2009). Neutrophil infiltration of cellular lipid membranes will result in lipid peroxidation reactions that produce free radicals. Free radicals can interfere with tissue integrity, mediate mucosal injury by causing degradation of epithelial basement membrane, cell metabolic changes and DNA damage. The presence of reactive oxidative species and prolonged gastric inflammation leads to the progression of chronic gastritis to chronic atrophic gastritis (Tan & Yeoh 2015). In addition, *H. pylori* with CagA (+) will inject CagA proteins directly into the cell via type IV secretion system. The CagA protein will undergo tyrosine phosphorylation by Src family kinase. Tyrosine phosphorylated CagA will bind to Src homology 2 (SHP2) containing tyrosine phosphatase (SHP-2) protein. The CagA-SHP2 complex will inactivate the focal adhesion kinase (FAK) that causes cell morphological transformation. In addition, the CagA-SHP2 complex will induce an abnormal mitogenic signal through the Erk MAP kinase cascade that leads to carcinogenesis (Kusters et al. 2006).

A family history of gastric cancer remained independently associated with gastric cancer (Masjedizadeh et al. 2013; Shin et al. 2010). Meta-analysis study showed that first-degree relatives of patients with gastric cancer might be at an increased risk for developing gastric cancer (Rokkas et al. 2010). Relatives of patients with gastric cancer have an increased prevalence of gastric premalignant lesion (El-Omar et al. 2013). This study also found that patients with a family history of gastric cancer significantly increased risk to have gastric premalignant lesion. Pathophysiology remains unclear, may be due to the influence of genetic factors, the same exposure to carcinogens (nitrogen, cigarette smoke, alcohol) among family members, same diet (high salt, smoked), hygiene level and *H. pylori* infection.

Effects of alcohol on gastric premalignant lesion are still controversial. This study found that alcohol significantly increased risk of having gastric premalignant lesion. Alcohol could cause some damage to gastric mucosa and induce chronic gastritis. In addition, alcohol could promote the absorption of carcinogen and decrease the detoxification activity of liver (Wu et al. 2013).

Smoking is a risk factor for gastric cancer. Nicotine substances that mutagenic can bind to the gastric mucosal DNA. N-nitroso-compound present in tobacco plays a role in gastric carcinogenesis process (Nishino et al. 2006; Nomura et al. 2012). Felley et al. (2012) and Liu et al. (2010) reported that smoking was a risk factor for gastric premalignant lesion. While there is another study showed that smoking did not associated with gastric premalignant lesion (den Hoed et al. 2011). The difference in results might be due to differences in the frequency of smoking, duration of smoking and type of cigarettes commonly used. However, this study found that there were no associations between use of NSAIDs and high salt diet with gastric premalignant lesion.

Finally, this study had shown that only *H. pylori* infection, family history of gastric cancer, alcohol intake and ethnicity were the key factors to predict the individual chance of developing premalignant gastric lesion. Identifying individuals at risk is important in surveillance and prevention of gastric premalignant lesion and gastric cancer.

Conclusion

Risk factors of gastric premalignant lesion were *H. pylori* infection, family history of gastric cancer, alcohol intake and Batak ethnic.

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