Urease Levels and Gastritis Stage in Dyspeptic Patients

Muhammad Miftahussurur[1,2,3*], Chyntia Dewi Maharani Putri[1], Titong Sugihartono[1], Ari Fahrial Syam[4], Herry Purbayu[1], Diah Priyantini[5], Hartono Kahar[6], Yudith Annisa Ayu Rezkitha[2,7], Iswan Abbas Nusi[1], Poernomo Boedi Setiawan[1], Ummi Maimunah[1], Langgeng Agung Waskito[2], Ulfa Kholili[1], Budi Widodo[1], Amie Vidyani[1], Husin Thamrin[1], Gontar A. Siregar[8], Reny I'tishom[9], Tomohisa Uchida[10], Yoshio Yamaoka[1,3]

[1] Division of Gastroentero-Hepatology, Department of Internal Medicine, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya 60286, Indonesia

[2] Helicobacter pylori and Microbiota Study Group Institute of Tropical Disease, Universitas Airlangga, Surabaya 60115, Indonesia

[3] Department of Environmental and Preventive Medicine, Oita University Faculty of Medicine, Yufu 879-5593, Japan

[4] Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, University of Indonesia, Jakarta 10430, Indonesia

[5] Faculty of Nursing, Universitas Airlangga, Surabaya 60115, Indonesia

[6] Department of Clinical Pathology, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya 60131, Indonesia

[7] Faculty of Medicine, Muhammadiyah University of Surabaya, Surabaya 60113, Indonesia

[8] Division of Gastroentero-Hepatology, Department of Internal Medicine, Faculty of Medicine, North Sumatra University, Medan, 20115, Indonesia

[9] Department of Medical Biology, Faculty of Medicine, Universitas Airlangga, Surabaya 60131, Indonesia

[10] Department of Molecular Pathology, Oita University Faculty of Medicine, Yufu 879-5593, Japan

Corresponding Author:

Muhammad Miftahussurur, MD., Ph.D. Division of Gastroentero-Hepatology, Department of Internal Medicine, Faculty of Medicine Universitas Airlangga - Dr. Soetomo Hospital. Jalan Mayjend Prof. Dr. Moestopo No. 6-8 Surabaya, Surabaya 60286, Indonesia. E-mail: muhammad-m@fk.unair.ac.id.

ABSTRACT

Background: *Dyspepsia is a frequent main symptom of inpatients and outpatients scenario in Indonesia. However, the number of endoscopy facilities are still low, thus the use of non-invasive method to detect gastritis is necessary. We measured the relationship between urease levels and the stage of gastritis in dyspeptic adult patients.* ***Methods:*** *A cross-sectional study included outpatient dyspepsia patient from November 2018 to February 2019. We examined ^{14C}-Urea Breath Test (UBT) and determined the stage of gastritis based on the Updated Sydney System classification.* ***Results:*** *The urease level of acute and chronic gastritis positive patients were higher than negative patients ($p = 0.001$, $r = 0.353$; $p < 0.0001$, $r = 0.433$, respectively). The AUC value of ^{14C}-UBT to detect acute, chronic, and atrophic gastritis are 0.889, 0.632 and 0.544, respectively. The best cut-off points of ^{14C}-UBT to predict acute gastritis was ≥26.50δ‰ with sensitivity and specificity being 88.89% and 63.95%, respectively. Whereas the best cut-off points for chronic gastritis was ≥34.50δ‰ with 82.89% sensitivity, 63.16% specificity. As for atrophic gastritis, it showed very low AUC value, hence it is not a sufficient test modality to predict atrophic gastritis cases.* ***Conclusion:*** *^{14C}-UBT is sufficient for predicting acute or chronic gastritis but not for atrophic gastritis.*

Keywords**:** *Dyspepsia, gastritis severity, urea breath test, cancer.*

INTRODUCTION

Dyspepsia is the most common gastrointestinal symptom in clinical practice.[1] Approximately 44.7% patients with dyspepsia had gastritis or duodenitis diagnosed by endoscopic examination in Indonesia.[2] Dyspepsia might be caused by two factors, infection and non-infection. Infection is mostly caused by *Helicobacter pylori*, whereas non-infection might be caused by stress, diet habits, hormonal factors and other functional factors.[3] Detection of *H. pylori* infection could be performed by many ways, such as histological examination, stool antigen test, anti *H. pylori* antibody and urea breath test (UBT).[4]

Gastritis, especially atrophic gastritis is the common contributing factor for gastric cancer.[5] Inflammation of the gastric mucosa may cause loss of glands that will eventually be replaced by intestinal-type epithelial cells, which is considered as a low-grade dysplasia.[6] This dysplastic tissue then become intestinal type gastric cancer as the end result of progressive changes in the gastric mucosa.[7] Mechanism of gastritis induced by urease enzyme activity remains unclear. Urea and urease may increase mucosal damage due to increased ammonia level in the gastric mucosa.[8] A study in mice given ammonia showed an increase in the number of inflammatory cells induced by chronic gastritis, suggesting a significant relationship between ammonia levels and gastritis.[9] Another study in patients with dyspepsia confirmed that ammonia levels were significantly associated with the severity of gastritis.[10] In addition, peptic ulcer patients had significantly higher urease level than patients without peptic ulcers.[11] It is suspected that there are urease-producing bacteria, including pathogens other than *H. pylori* which cause chronic gastritis in areas with low prevalence of *H. pylori* such as Indonesia. UBT is a non-invasive method to detect *H. pylori* which relied on the fact that *H. pylori* secretes urease enzyme which converts urea into ammonia and carbon dioxide.[12,13] The UBT is a reliable method to detect *H. pylori* and performed based on the ability of *H. pylori* to break down urea, which is absorbed from the stomach and eliminated in exhalation.[14] If the isotope is detected in the breath, the test is positive, suggesting *H. pylori* presence in the stomach.[15] The amount of urease activity, detected by value from UBT may reflect the *H. pylori* bacterial load in the stomach.[16] Indeed, UBT is mainly used for detecting *H. pylori*, but since there are other bacteria that has urease activity, such as *Proteus mirabilis*, *Citrobacter freundii*, *Klebsiella pneumoniae*, *Enterobacter cloacae* and *Staphylococcus aureus*).[17] However, the end point of urease activity is producing ammonia, a toxic substance for the stomach. Therefore, UBT may have potential usage and become a non-invasive alternative diagnostic modality to detect urease-related gastritis.

Indonesia is a multi-ethnic country with over 267 million people living in more than seventeen thousand islands with regional disparities in health service quality.[18] Dyspepsia and gastritis are included in the top 10 diseases and is common in inpatients and outpatients clinics of Indonesia. However, the number of endoscopy experts in Indonesia is lacking and the number of endoscopy centers is still low.[19] Recently, ^{14}C-UBT, a non-invasive method with simple, less expensive, accurate and easy handling is massively used in clinical practice. This study aimed to determine relationship between urease levels with the severity of gastritis in dyspeptic patients.

METHODS

We conducted a cross sectional study from November 2018 to February 2019 in Dr. Soetomo Teaching Hospital, Surabaya, Indonesia. Ninety five dyspeptic patients aged 18 to 70 years old were included in this study. We excluded patients receiving antibiotics and bismuth drugs 4 weeks prior to examination, proton pump inhibitor 2 weeks prior to examination, patients with history of gastric surgery, bleeding gastrointestinal tract within 4 weeks, impaired kidney diseases, liver cirrhosis, diabetes mellitus, gut malignancy, history of smoking and alcohol consumption, history of NSAID consumption and patients with endoscopy contraindication. We collected demographics data and dietary habits by questionnaire.

One day before endoscopy, all patients were examined by ^{14}C-UBT (Heliprobe, Stockholm,

Sweden) using ^{14}C-urea (250 uCi, Amersham) reconstituted with 25 ml of sterile distilled water. Subjects were fasted for at least six hours prior to the test. They removed false teeth (if present), and cleansed their mouth with antiseptic solution such as thymol, salol, menthol, saccharin, fuchsin, water and ethanol. A baseline breath sample was collected and identified as time 0. Then, they swallowed 5 uCi of ^{14}C-urea dissolved in 20 ml of water. Breath samples were collected at 5, 10, 15, 20 and 30 minutes. Patients were instructed to blow through tubing attached to a safety trap into a scintillation vial containing 2.5 ml of 400 mM Hyamine (Sigma) in methanol with 15 mg/l thymolphthalein (blue alkaline color). They had to blow until the solution became colorless indicating the collection of 1 mmol of CO_2. Once the breath samples had been collected, scintillation fluid (10 ml-5.5 g PPO/0.2g POPOP of 2:1 v/v Toluene/Triton-X) was added to the vial; counting proceeded for 5 minutes per vial, and the results were expressed as cpm/mmol CO_2. Counting efficiency of the Beckman LS 10^{0}C was 93%.

Endoscopy and biopsy were performed on the next day. Experienced endoscopists collected single biopsy samples from corpus and antrum of the gaster for histological examination. Patients with evidence of activity or inflammation in the antrum or corpus upon histological examination were considered positive for gastritis. The severity of gastritis is determined by histological examination based on the updated Sydney system classification.[20] Informed consent was obtained from all participants, and the protocol was approved by the Ethics Committee of Dr. Soetomo Teaching Hospital (Surabaya, Indonesia).

Statistical Analysis

Statistical Analysis is done using the SPSS statistical software package version 23 (SPSS, Inc., Chicago, IL, USA). Correlation analysis used Spearman's Signed Rank Test because the distribution data was abnormal. Correlation coefficient considered with r and significant analysis with *P* value was <0.05. In addition, to determine the cut-off point of UBT examination we used Receiver Operating Characteristic (ROC) analysis for showing area under curve (AUC) then we calculated the sensitivity and specificity from the determined cut-off point.

RESULTS

Demographical Characteristics of Patients

The total study population was 95 consecutive dyspeptic patients (52 female and 43 male; age range 20-65 years). Female patients had a higher proportion of chronic and atrophic gastritis (4/52, 7.7%; and 15/52, 28.8%, respectively, **Table 1**), however statistically insignificant (p = 0.130). Age group of >60 years old had a more acute gastritis than other age groups (6/21, 28.6%, p = 0.018). Christian (5/20, 25.0%) and Buddhist (1/3, 33.3%) patients had higher association with acute gastritis (p = 0.038). However, there was no association between marital status, job, income, education and ethnics with prevalence of gastritis (all p >0.05).

The amount of resident 1–4 people had higher proportion in acute and chronic gastritis (7/71, 9.9%, p = 0.049 and 15/71, 21.1%, p =

Table 1. Demographical Characteristic of Respondents

Demographical Characteristic	n	Acute Gastritis	Chronic Gastritis	Atrophic Gastritis
Sex				
Male	43	5 (11.6)	6 (14.0)	9 (20.9)
Female	52	4 (7.7)	13 (25.0)	15 (28.8)
Age				
20-29 years old	4	0 (0.0)	1 (25)	2 (50.0)*
30-39 years old	9	0 (0.0)	0 (0.0)	0 (0.0)
40-49 years old	31	2 (6.5)	5 (16.1)	4 (12.9)
50-59 years old	30	1 (3.3)	5 (16.1)	10 (33.3)
>60 years old	21	6 (28.6)*	8 (38.1)	8 (38.1)
Marital Status				
Married	87	9 (10.3)	18 (20.7)	21 (24.1)
Single	8	0 (0.0)	1 (12.5)	3 (37.5)

Job				
Civil Servant	5	0 (0.0)	0 (0.0)	1 (20.0)
Housewife	35	2 (5.7)	7 (20.0)	9 (25.7)
Employee	42	5 (11.9)	8 (19.0)	11 (26.2)
Doctor	1	0 (0.0)	0 (0.0)	0 (0.0)
Teacher	2	0 (0.0)	1 (50.0)	0 (0.0)
Student	2	0 (0.0)	0 (0.0)	0 (0.0)
Retired	2	0 (0.0)	1 (50.0)	0 (0.0)
Farmer	6	2 (2.1)	2 (33.3)	3 (50.0)
Income				
Under Minimum Regional Income**	69	6 (8.7)	15 (21.7)	16 (23.2)
Upper Minimum Regional Income**	26	3 (11.5)	4 (15.4)	8 (30.8)
Religion				
Buddhism	3	1 (33.3)*	1 (33.3)	1 (33.3)
Hindu	2	0 (0.0)	0 (0.0)	0 (0.0)
Moeslim	65	3 (4.6)	10 (15.4)	13 (20.0)
Catholic	5	0 (0.0)	1 (20.0)	2 (40.0)
Christian	20	5 (25.0)	7 (35.0)	8 (40.0)
Education				
Not educated	1	0 (0.0)	0 (0.0)	0 (0.0)
Elementary school	9	1 (11.1)	2 (22.2)	2 (22.2)
Junior high school	13	2 (15.4)	5 (38.5)	7 (53.8)
Senior high school	43	2 (4.7)	7 (16.3)	8 (18.6)
Diploma	2	0 (0.0)	0 (0.0)	1 (50.0)
Bachelor	25	4 (16.0)	5 (20.0)	6 (24.0)
Master	2	0 (0.0)	0 (0.0)	0 (0.0)
Ethnic				
Ambon	2	0 (0.0)	0 (0.0)	1 (50.0)
Bataknese	22	5 (22.7)	6 (27.3)	7 (31.8)
Javanese	49	2 (4.1)	9 (18.4)	10 (20.4)
Madura	4	0 (0.0)	0 (0.0)	1 (25.0)
Sunda	1	0 (0.0)	0 (0.0)	0 (0.0)
Tioghoa	11	2 (18.2)	4 (36.4)	5 (45.5)
Alas	1	0 (0.0)	0 (0.0)	0 (0.0)
Balinese	3	0 (0.0)	0 (0.0)	0 (0.0)
Padang	1	0 (0.0)	0 (0.0)	0 (0.0)
Pak Pak	1	0 (0.0)	0 (0.0)	0 (0.0)

* p <0.05 with chi-square analysis
** USD 272 currency on March 2020

0.031, respectively, **Table 2**), but only tended in atrophic gastritis (19/71, 26.8%, p = 0.094). The frequency of eating with hand had association with acute, chronic and atrophic gastritis (p = 0.026, p = 0.045 and p = 0.036, respectively). Smokers had higher prevalence of acute gastritis than non-smokers (5/22, 22.7% vs. 4/73, 5.5%, p = 0.015). Source of water, alcohol drinker, hand washing after toilet use and before eating did not influence prevalence of gastritis (all p >0.05).

Among 95 subjects, 19 (26.3%) frequently consumed analgesics and had association with acute gastritis (p = 0.005, **Table 3**). In addition, anxiolytic users had a higher acute gastritis rather than non-users (5/26, 19.2% vs. 4/69, 5.8%, p = 0.045). The most six common symptoms in acute, chronic and atrophic gastritis were epigastric pain (9/92, 9.8%; 14/92, 20.3%; 23/92, 24.2%, respectively), easy to feel full when consuming food or drink (8/64, 12.5%; 16/64, 25.0%; 17/64, 26.6%, respectively), nausea (6/64, 9.4%; 12/64, 18.8%; 15/64, 23.4%, respectively), feeling bloated (6/69, 8.7%; 14/69, 20.3%; 16/69, 23.2%, respectively), heart burn (4/46, 8.7%; 8/46, 17.4%; 13/46, 28.3%, respectively) and vomiting (7/72, 9.7%; 14/72, 19.4%; 16/72, 22.2%, respectively), but there was no significant association between all symptoms with gastritis (all p >0.05).

There were three most comon diseases from endoscopy including erosive gastritis (20/95, 21.1%), gastroesophageal reflux disease (18/95, 18.9%) and superficial gastritis (13/95, 13.7%). The prevalence of *H. pylori*-positive subjects in this study was very low (4/48, 8.3%). When we used the cut-off point of UBT from manual

Table 2. Health Behavior of Subjects

Health Behavior	n	Acute Gastritis	Chronic Gastritis	Atrophic Gastritis
Resident in One House				
1 – 4 people	71	7 (9.9)*	15 (21.1)*	19 (26.8)
5 and more people	24	2 (8.3)	4 (16.7)	5 (20.8)
Source of Water				
Well	8	0 (0.0)	0 (0.0)	1 (12.5)
New Mineral Water	14	1 (7.1)	1 (7.1)	3 (21.4)
Refill Mineral Water	48	4 (8.3)	11 (22.9)	14 (29.2)
Boiled Water	25	4 (16.0)	7 (28.0)	6 (24.0)
Hand Wash After Toilet				
Never	1	0 (0.0)	0 (0.0)	0 (0.0)
Rarely	6	0 (0.0)	1 (16.7)	2 (33.3)
Sometimes	9	1 (11.1)	3 (33.3)	3 (33.3)
Often	25	2 (8.0)	2 (8.0)	6 (24.0)
Always	54	6 (11.1)	13 (24.1)	13 (24.1)
Hand Wash Before Eat				
Never	1	0 (0.0)	0 (0.0)	0 (0.0)
Rarely	3	0 (0.0)	0 (0.0)	1 (33.3)
Sometimes	13	2 (15.4)	3 (23.1)	3 (23.1)
Often	35	3 (8.6)	5 (14.3)	10 (28.6)
Always	43	4 (9.3)	11 (25.6)	10 (23.3)
Eating with Hand				
Never	7	1 (14.3)	1 (14.3)	2 (28.5)
Rarely	24	3 (12.5)	8 (33.3)	7 (29.2)
Sometimes	31	0 (0.0)	2 (6.5)	6 (19.4)
Often	20	1 (5.0)	3 (15.0)	4 (20.0)
Always	13	4 (30.8)*	5 (38.5)*	5 (38.5)*
Smoking				
Yes	22	5 (22.7)*	5 (22.7)	4 (18.2)
No	73	4 (5.5)	14 (19.2)	20 (27.4)
Alcohol				
Yes	21	4 (19.0)	5 (23.8)	5 (23.8)
No	74	5 (6.8)	14 (18.9)	19 (25.7)

** p <0.05 with chi-square analysis*

Table 3. Medical Status of Subjects

Medical Status	n	Acute Gastritis	Chronic Gastritis	Atrophic Gastritis
Symptom				
Bloated				
Yes	69	6 (8.7)	14 (20.3)	16 (23.2)
No	26	3 (11.5)	5 (19.2)	8 (30.8)
Epigastric pain				
Yes	92	9 (9.8)	18 (19.6)	23 (24.2)
No	3	0 (0.0)	1 (33.3)	1 (33.3)
Heart Burn				
Yes	46	4 (8.7)	8 (17.4)	13 (28.3)
No	49	5 (10.2)	11 (22.4)	11 (22.4)
Nausea				
Yes	64	6 (9.4)	12 (18.8)	15 (23.4)
No	31	3 (9.7)	7 (22.6)	9 (29.0)
Vomiting				
Yes	23	2 (8.7)	5 (21.7)	8 (34.8)
No	72	7 (9.7)	14 (19.4)	16 (22.2)
Easy to fill				
Yes	64	8 (12.5)	16 (25.0)	17 (26.6)
No	31	1 (3.2)	3 (9.7)	7 (22.6)
Proton Pump Inhibitor				
Yes	4	1 (25.0)	2 (50.0)	1 (25.0)
No	91	8 (8.8)	17 (18.7)	23 (25.3)
Antibiotics				
Yes	11	2 (18.2)	4 (36.4)	2 (18.2)
No	84	7 (8.3)	15 (17.9)	22 (26.2)

Analgesic				
Yes	19	5 (26.3)*	5 (26.3)	4 (21.1)
No	76	4 (5.3)*	14 (18.4)	20 (26.3)
Anti-anxiety				
Yes	26	5 (19.2)*	6 (23.1)	7 (26.9)
No	69	4 (5.8)*	13 (18.8)	17 (24.6)

** p <0.05 with chi-square analysis*

instruction (50.00), there was no correlation between diseases and positivity of *H. pylori*.

Urease Levels and Stage of Gastritis

Based on the gastritis stage, we observed a significant trend of increasing UBT level with both degree of acute and chronic antral gastritis (r= 0.366 and r= 0.404, respectively; both P < 0.001) (**Figure 1**). However, we could not find correlation between degree of both atrophic gastritis and intestinal metaplasia in antrum. As for in the corpus, we only could find a significant correlation between corporal atrophy and UBT level (r= 0.270, P=0.036). The others histological parameter (acute gastritis, chronic gastritis and intestinal metaplasia) did not show a significant association (all P > 0.05).

We validated the accuracy of ^{14}C-UBT to predict acute gastritis. Acute gastritis is expressed as a neutrophil infiltration ≥1 on the gastric mucosa. The AUC of the urea levels compared with acute gastritis with AUC score was 0.889 (95% CI = 0.729 – 0.950) (**Figure**

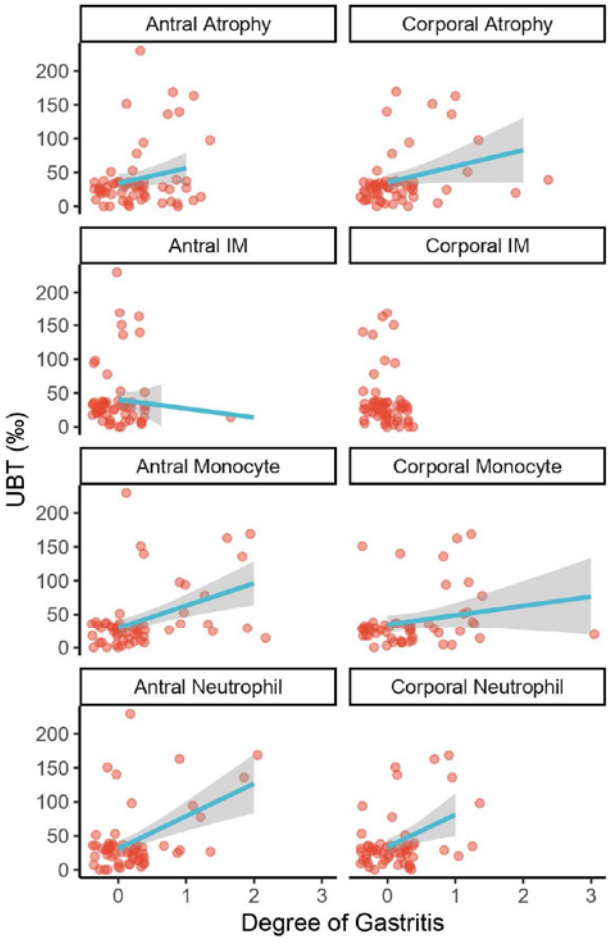

Figure 1. Association between urease levels with the degree of gastritis in each stage.

2). The best cut-off point was ≥26.50 δ‰ with sensitivity of 88.89%, specificity of 63.95%, positive predictive value (PPV) of 71.15%, negative predictive value (NPV) of 85.20%, positive likelihood ratio of 2.47, negative likelihood ratio of 0.17 and accuracy of 76.42%.

In addition, we also determine the performance of ^{14}C-UBT for detecting chronic gastritis. UBT level yielded an AUC score of 0.632 (95% CI = 0.592 – 0.883) (**Figure 3**). The best cut-off point was ≥34.50 δ‰ with sensitivity, specificity, PPV, NPV, positive likelihood ratio and negative likelihood ratio being 82.89%, 63.16%, 78.69%, 69.23%, 3.69, and 0.44, respectively with overall 73.03% accuracy.

The validation examination for atrophic gastritis showed a very low AUC score of 0.544 (95% CI = 0.396 – 692). Therefore, it is not sufficient for determining the best cut-off. As for the accuracy of the ^{14}C UBT for intestinal metaplasia was not measured because there were only 2 positive cases.

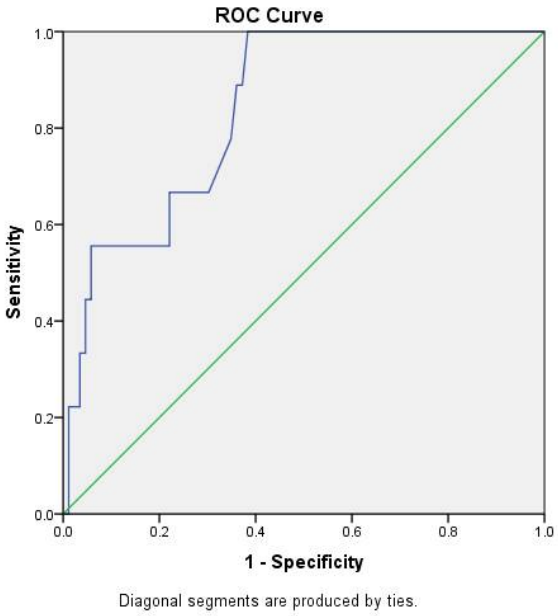

Figure 2. The urea levels compared with acute gastritis with AUC score.

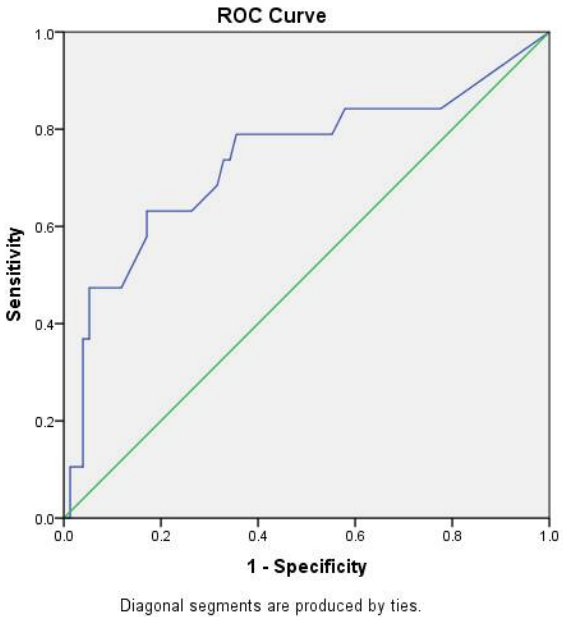

Figure 3. Urease activity level compared to chronic gastritis resulted AUC score.

DISCUSSION

We confirmed the accuracy of ^{14}C-UBT to predict severity of gastritis but not for atrophic gastritis. The cut-off point ^{14}C-UBT to measure acute and chronic gastritis were higher than atrophic gastritis. This result is in agreement with a previous study which showed that the UBT value was correlated to gastric cancer and was significantly lower than that for gastritis, duodenal ulcer, or gastric ulcer in *H. pylori*-positive patients.[21,22] They also found a low UBT value were associated with the risk of gastric cancer, similar with this study where the cut-off points in atrophic was lower than acute or chronic gastritis.[16]

Urease level has better sensitivity in acute and chronic gastritis than atrophic gastritis due to the difference in *H. pylori* colonization bacterial load. Extensive gastric mucosal atrophy may decrease colonization by *H. pylori* and produce a low UBT value.[4,23] In addition, UBT value is mainly influenced by *H. pylori* colonization which lead to increasing neutrophil infiltration, therefore it contribute to the higher association between acute gastritis rather than the atrophic gastritis.[24,25] However, Indonesia has a low prevalence of *H. pylori* infection.[26] In this study, we also confirmed that

the prevalence of *H. pylori* infection was very low, suggesting in Indonesian cases generally the bacteria do not have a major influence on clinical outcomes[27], especially in ethnic groups with low prevalence of *H. pylori*. Therefore, due to dyspepsia and gastritis being one of the top 10 diseases in Indonesia, non-*H. pylori* urease-producing bacteria might a major role causing gastritis. Non-*H. pylori* bacteria such as non-*H. pylori Helicobacter spp., Mycobacterium spp., Staphylococcus spp, Proteus mirabilis*, *Citrobacter freundii*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*. could produce urease enzyme.[17,25]

Sufficient sensitivity but low specificity of ^{14}C-UBT for determining acute gastritis, suggests that ^{14}C-UBT has sufficient ability to screen for acute gastritis, but low specificity indicates UBT test was not a good diagnostic method.[28,29] Thus, other modalities, either invasive or non-invasive to determine gastritis is necessary. There were options for non-invasive diagnostic method that had potential determining the gastritis status, such as serum pepsinogen level. Serum pepsinogen had been well recognized as a non-invasive screening option for early stages of gastric cancer. Combination of serum pepsinogen and anti-*H. pylori* antibody, Miki and co-workers had established a stratification method for gastric cancer risk.[30] That method had been applied and showed promising results in several populations, including in Indonesia.[31,32] Therefore, serum pepsinogen might be still become the best non-invasive methods to measure severity of gastritis, especially in Indonesia.[33]

Urease exposure can cause an inflammatory reaction by producing reactive oxygen species and inducing the expression of inducible NO-synthesizing enzyme.[34] Urease can also give a toxic effect indirectly by producing ammonia, a product of urea hydrolysis.[16] The presence of ammonia in the stomach can cause hypoxia in gastric tissue by increasing intracellular and intra mitochondrial pH. Ammonia also interferes with the activity of tricarboxylic acid which can reduce ATP synthesis so that it interferes with cell migration and cell proliferation which can inhibit repair of the gastric epithelium. This activity causes the activation of the danger associated molecular pattern (DAMP) that recognized by the pattern recognition receptor and activate monocytes and neutrophils and the recruitment of inflammatory cells, such as IL-1, IL-8 and TNF-αv.[35] In addition to inducing the release of proinflammatory cytokines, ammonia can also enter the G cell nucleus easily and bind the gene-regulating gastrin unit so that it can activate expression and enhance gastrin formation.[36] That mechanism might be a responsible way explaining observed gastritis in the high ammonia individuals.

Based on demographic characteristics, age group of >60 years old had higher acute gastritis prevalence than other age groups because ageing reductes of mucous cells in the gastric mucosa of elderly, which is associated with a decreasing prostaglandin concentration.[26] The research finding also stated smokers had higher prevalence of acute gastritis than non-smokers, and it is in agreement with other studies.[15] Smokers have higher cases in gastritis because the gaster produce higher amounts of acid than in non-smokers. Female patients were found to have higher prevalence of chronic and atrophic gastritis, but it is statistically insignificant. Some authors support a small contribution of sex differences where there is predominance in *H. pylori* related outcomes in males, including gastric cancer.

There were several limitations in this current study, first it had a very low sample number and was only collected in one center. In addition, there was no healthy individuals that were included in the population. Therefore, interpretation warrants caution since it may not represent the whole Indonesian population. Our study did not have any information regarding *H. pylori* status which might be considered as a main factor affecting the value of ^{14}C-UBT, since urease is currently believed to mainly come from bacterial infection; therefore, the association between UBT and gastritis might be affected by *H. pylori*. This condition is needed a careful consideration.

CONCLUSION

Our study showed UBT has a sufficient potential for predicting acute and chronic antral

gastritis with a good value of sensitivity. As for other gastritis parameters, UBT showed not a good choice for predicting those stages. The UBT mainly used for determining *H. pylori* infection; therefore, the involvement of *H. pylori* infection in the development of gastritis still need to be carefully considered.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interests.

REFERENCES

1. Suzuki H, Moayyedi P. Helicobacter pylori infection in functional dyspepsia. Nat Rev Gastroenterol Hepatol. 2013;10(3):168–74.
2. Oling M, Odongo J, Kituuka O, Galukande M. Prevalence of Helicobacter pylori in dyspeptic patients at a tertiary hospital in a low resource setting Surgery. BMC Res Notes. 2015;8(1):4–9.
3. Talley NJ. Functional dyspepsia: New insights into pathogenesis and therapy. Korean J Intern Med. 2016;31(3):444–56.
4. Miftahussurur M, Yamaoka Y. Diagnostic methods of Helicobacter pylori infection for epidemiological studies: Critical importance of indirect test validation. Biomed Res Int. 2016;2016.
5. Yoshida H, Agnes RD, Solle M, Jayadi M. A long-term evaluation of families affected by the Bili-Bili Dam development resettlement project in South Sulawesi, Indonesia. Int J Water Resour Dev. 2013;29(1):50–8.
6. Correa P. Gastric cancer: overview. Gastroenterol Clin North Am. 2013;42(2):211–7.
7. Van Cutsem E, Sagaert X, Topal B, Haustermans K, Prenen H. Gastric cancer. Lancet. 2016;388(10060):2654–64.
8. Zhang P, Yang M, Zhang Y, et al. Dissecting the single-cell transcriptome network underlying gastric premalignant lesions and early gastric cancer. Cell Rep. 2019;27(6):1934-1947.e5.
9. Rahmani A, Moradkhani A, Hafezi Ahmadi MR, et al. Association between serum levels of high sensitive C-reactive protein and inflammation activity in chronic gastritis patients. Scand J Gastroenterol. 2016;51(5):531–7.
10. Siddiqui MK, Nurdin, Baskoro ET. Total edge irregularity strength of the disjoint union of helm graphs. J Math Fundam Sci. 2013;45(2):163–71.
11. Massironi S, Zilli A, Elvevi A, Invernizzi P. The changing face of chronic autoimmune atrophic gastritis: an updated comprehensive perspective. Autoimmun Rev. 2019;18(3):215–22.
12. Di Rienzo TA, D'Angelo G, Ojetti V, et al. 13C-Urea breath test for the diagnosis of Helicobacter pylori infection. Eur Rev Med Pharmacol Sci. 2013;17(Suppl 2):51–8.
13. Siddique I, Al-Qabandi A, Al-Ali J, et al. Association between Helicobacter pylori genotypes and severity of chronic gastritis, peptic ulcer disease and gastric mucosal interleukin-8 levels: Evidence from a study in the Middle East. Gut Pathog. 2014;6(1):1–10.
14. Best L, Takwoingi Y, Siddique S, et al. Non-invasive diagnostic tests for Helicobacter pylori infection. Cochrane Database Syst Rev. 2018;(3):CD012080.
15. Ferwana M, Abdulmajeed I, Alhajiahmed A, et al. Accuracy of urea breath test in Helicobacter pylori infection: Meta-analysis. World J Gastroenterol. 2015;21(4):1305–14.
16. Morgan DR, Torres J, Sexton R, et al. Risk of recurrent helicobacter pylori infection 1 year after initial eradication therapy in 7 Latin American communities. JAMA - J Am Med Assoc. 2013;309(6):578–86.
17. Osaki T, Mabe K, Hanawa T, Kamiya S. Urease-positive bacteria in the stomach induce a false-positive reaction in a urea breath test for diagnosis of Helicobacter pylori infection. J Med Microbiol. 2008;57(7):814–9.
18. Miftahussurur M, Syam AF, Makmun D, et al. Helicobacter pylori virulence genes in the five largest islands of Indonesia. Gut Pathog. 2015;7(1).
19. Makmun D. Present status of endoscopy, therapeutic endoscopy and the endoscopy training system in Indonesia. Dig Endosc Off J Japan Gastroenterol Endosc Soc. 2014;26 Suppl 2:2–9.
20. Hassan TM, Al-Najjar S, Al-Zahrani I, Alanazi FB, Alotibi M. Helicobacter pylori chronic gastritis updated Sydney grading in relation to endoscopic findings and H. pylori IgG antibody: diagnostic methods . J Microsc Ultrastruct. 2016;4(4):167.
21. De Re V, Orzes E, Canzonieri V, et al. Pepsinogens to distinguish patients with gastric intestinal metaplasia and helicobacter pylori infection among populations at risk for gastric cancer. Clin Transl Gastroenterol. 2016;7(7).
22. Tanaka T, Mulyadi IK, Moestikaningsih, et al. Rare Helicobacter pylori infection may explain low stomach cancer incidence: Ecological observations in Bali, Indonesia. Asian Pacific J Cancer Prev. 2016;17(3):979–84.
23. Miftahussurur M. Noninvasive Helicobacter pylori diagnostic methods in Indonesia. Vol. 14. Gut and liver. Editorial Office of Gut and Liver; 2020. p. 553–9.
24. Ivashkin VT, Kasoev SG, Stepanov EV. Analysis of the isotopic composition of exhaled air by the diode laser spectroscopy method in the 2-μm region for diagnosis of Helicobacter pylori-associated diseases. Opt Spectrosc. 2019;126(6):710–20.
25. Mitchell H, Katelaris P. Epidemiology, clinical impacts and current clinical management of helicobacter pylori infection. Med J Aust. 2016;204(10).
26. Syam AF, Miftahussurur M, Makmun D, et al. Risk

factors and prevalence of Helicobacter pylori in five largest islands of Indonesia: A preliminary study. PLoS One. 2015;10(11):1–14.
27. Miftahussurur M, Syam AF, Makmun D, et al. Helicobacter pylori virulence genes in the five largest islands of Indonesia. Gut Pathog. 2015;7(1):1–10.
28. Ateshkadi A, Lam NP, Johnson CA. Helicobacter pylori and peptic ulcer disease. Vol. 12. Clinical Pharmacy; 1993. p. 34–48.
29. Currie LA, Eglinton TI, Benner BA, Pearson A. Radiocarbon "dating" of individual chemical compounds in atmospheric aerosol: First results comparing direct isotopic and multivariate statistical apportionment of specific polycyclic aromatic hydrocarbons. Nucl Instruments Methods Phys Res Sect B Beam Interact with Mater Atoms. 1997;123(1–4):475–86.
30. Miki K, Morita M, Sasajima M, Hoshina R, Kanda E, Urita Y. Usefulness of gastric cancer screening using the serum pepsinogen test method. Am J Gastroenterol. 2003;98(4):735–9.
31. Tong Y, Wu Y, Song Z, Yu Y, Yu X. The potential value of serum pepsinogen for the diagnosis of atrophic gastritis among the health check-up populations in China: a diagnostic clinical research. BMC Gastroenterol. 2017;17(1):88.
32. Miftahussurur M, Agung Waskito L, Aftab H, et al. Serum pepsinogens as a gastric cancer and gastritis biomarker in South and Southeast Asian populations. PLoS One. 2020;15(4).
33. Agkoc M, Dursun H, Albayrak F, et al. Usefulness of serum pepsinogen levels as a screening test for atrophic gastritis and gastric cancer. Eurasian J Med. 2010;42(1):15–8.
34. Uski O, Jalava PI, Happo MS, et al. Effect of fuel zinc content on toxicological responses of particulate matter from pellet combustion in vitro. Sci Total Environ. 2015;511:331–40.
35. Kwiecien S, Jasnos K, Magierowski M, et al. Lipid peroxidation, reactive oxygen species and antioxidative factors in the pathogenesis of gastric mucosal lesions and mechanism of protection against oxidative stress - induced gastric injury. J Physiol Pharmacol. 2014;65(5):613–22.
36. Harada Y, Harada Y, Elly C, et al. Transcription factors Foxo3a and Foxo1 couple the E3 ligase Cbl-b to the induction of Foxp3 expression in induced regulatory T cells. J Exp Med. 2010;207(7):1381–91.