Urease Levels and Gastritis Severity in Dyspeptic Patients

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ABSTRACT

Introduction: Dyspepsia and gastritis are frequent in inpatients and outpatients clinics of Indonesia. However, the number of endoscopy centers is still low, thus the use of non-invasive method is necessary to detect gastritis. We determined relationship between urease levels measured with the severity of gastritis on in adult patients with dyspepsia.

Methods: A cross-sectional study included outpatient dyspepsia patient from November 2018 to February 2019. We examined ^{14}C-UBT and determined the severity 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 and p <0.0001, r = 0.433, respectively). The best cut-off points of ^{14}C UBT to predict acute gastritis was 26.50 with sensitivity 88.89%, specificity 63.95% with AUC score was 0.889. The best cut-off points for chronic gastritis was 34.50 with sensitifity 82.89%, specificity 63.16% and AUC score 0.632. The best cut-off point for atropic gastritis was 22.50 with sensitivity 54.17%, specificity 54.93 and AUC score 0.544.

Conclusion: ^{14}C-UBT is sufficient for predicting acute or chronic gastritis but not for atrophic gastritis.

Keywords: Dyspepsia, Gastritis severity, Urea Breath Test

Introduction

Dyspepsia is the most common gastrointestinal symptom in clinical practice (1). Approximately 44.7% patients with dyspepsia had gastritis or duodenitis from endoscopic examination in Indonesia (2). *Helicobacter pylori* secretes urease enzyme cause chronic inflammation of gastric mucosa and detected by urea breath test (UBT) (3). The UBT is a high accuracy methods to detect *H. pylori* and performed based on the ability of *H. pylori* to break down urea, then, absorbed from the stomach and eliminated in the breath (4). If the isotope is detected in the breath, the test is positive, suggesting *H. pylori* is present in the stomach (5).

Gastritis is the common contributing factor for gastric cancer (6). Intestinal type of gastric cancer was the end result of progressive changes in the gastric mucosa, starting from chronic gastritis, followed by multifocal atrophic gastritis and intestinal metaplasia (7). The next stage in the cascade is the loss of glands that eventually may be replaced by epithelium with intestinal phenotype and considered as a low-grade dysplasia (8). Mechanism of gastritis induced by urease enzyme activity remains unclear. Urea and urease may increased mucosal damaged due to increased ammonia level in the gastric mucosa (9). 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 (10). Another study in patients with dyspepsia confirmed that ammonia levels were significantly associated with the severity of gastritis (11). In addition, urease levels in patients with peptic ulcer were higher than in patients without peptic ulcer (12).

Indonesia is a multi-ethnic country consists over 267 million people living in more than seventeen thousand islands with regional disparities in health service quality (13). Dyspepsia and gastritis are top 10 diseases and still common in inpatients and outpatients clinics of Indonesia (14). However, the number of endoscopy experts in Indonesia is lacking and the

number of endoscopy centers is still low (15). Recently, ^{14}C UBT is a non-invasive method with simple, less expensive, accurate and easy handling, suggesting potentially to use as an alternative method to detect gastritis. This study aimed to determine relationship between urease levels with the severity of gastritis in dyspeptic patients.

METHODS

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

One day before endoscopy, all patients were examined ^{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 min. 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 min per vial, and the results were expressed as cpm/mmol CO2. Counting efficiency of the Beckman LS 100C was 93%.

Endoscopy and biopsy were performed on the next day. Experienced endoscopists collected biopsies from 1 corpus and 1 antrum 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 determine by histological examination based on the updated Sydney system classification. 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

The SPSS statistical software package version 23 (SPSS, Inc., Chicago, IL, USA) was used for data analysis. Correlation analysis used Chi-square because the distribution data was abnormal. Correlation coefficient considered with r andsignificant analysis with *P* value was <0.05. We also measured with Receiver Operating Characteristic (ROC) for showing area under cuver (AUC), cut-off point, sensitivity and specificity from the diagnostic test.

RESULTS

Demographical Characteristics of Respondents

Female patients were higher proportion suffered chronic and arophic gastritis (4/52, 7.7%; and 15/52, 28.8%, respectively, Table 1), however it was an unsignificant statistic (p = 0.130). Aged group >60 years old had a higher acute gastritis than other aged groups (6/21, 28.6%, p = 0.018). Christian (5/20, 25.0%) and Buddhism (1/3, 33,3%) religions had higher association with acute gastritis (p = 0.038). However, there was no association between marital status, job, income, education and ethnics with gastritis (all p >0.05).

The ammount 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 = 0.031, respectively, Table 2), but only tended in athropic 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, 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 wash after use toilet and before eat were not give influence to the prevalence of gastritis (all p >0.05).

Among 95 subjects, 19 (26.3%) frequent consumpted analgesic and had association with acute gastritis (p = 0.005, Table 3). In addition, anti-anxiety 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 fill when get 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), 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 was three most diseases from endoscopy

including erosive gastritis (20/95, 21.1%), gastroesofageal refluks disease (18/95, 18.9%) and superficial gastritis (13/95, 13.7%). When we used the cut-off point of UBT from manual instruction (50.00), there was no correlation between diseases and positivity of *H. pylori*.

Urease Levels and Severity of Gastritis

Based on UBT test, the urease level of acute gastritis positive patients were higher than negative patients (9/95, 9.5% vs. 86/95, 90.5%, $p = 0.001$, r = 0.353). In addition, the chronic gastritis positive patients were also higher than negative patients (19/95, 20.0% vs.76/95, 80.0%, $p < 0.0001$, r = 0.433).

We validated the accuracy of ^{14}C UBT to predict acute gastritis. The best cut-off point was 26.50 with sensitivity 88.89%, specificity 63.95%, positive predictive value 71.15%, negative predictive value 85.20%, positive likelihood ratio 2.47, negative likelihood ratio 0.17 and accuracy 76.42%. For further analysis, we used ROC analysis to determine the AUC of the urea levels compared with acute gastritis (Figure 1) with AUC score was 0.889.

Whilst, for chronic gastritis, we determined the best cut-off point was 34.50 with sensitifity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio were 82.89%, 63.16%, 78.69%, 69.23%, 3.69, and 0.44, respectively with total accuracy was 73.03%. Urea levels compared to the gold standard chronic gastritis resulted AUC score 0.632 (Figure 2).

The urease level of atrophic gastritis positive patients were higher than negative patients (24/95, 25.3% vs. 71/95, 74.7%, $p = 0.038$, r = 0.213). The results different with intestinal metaplasia has positive case just in 2 patients. The results of positive urease level lesss than negative (2/95, 2.1% vs. 93/95, 97.9%, $p = 0.180$, r = 0.198). For atrophic gastritis, the best cut-off point was 22.50 with sensitivity 54.17%, specificity 54.93%, positive predictive value 54.58%, negative predictive value 54.51%, positive likelihood ratio 1.20,

negative likelihood ratio 0.83 and accuracy 54.55% (Figure 3). The accuracy of the ^{14}C UBT for intestinal metaplasia was not measured because the positive case only 2 patients.

DISCUSSION

We confirmed the accuracy of ^{14}C-UBT to predict severity 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 concordances with previous study that the UBT value related to gastric cancer and significantly lower than that for gastritis, duodenal ulcer, or gastric ulcer in *H. pylori*-positive patients (16,17). They also found a low UBT values were associated with the risk of gastric cancer, as similar with this study that the cut-off points in atrophic was lower than acute or chronic gastritis (18).

Urease level has better sensitivity in acute or chronic gastritis than atrophic gastritis due to the different of *H. pylori* colonization number. Extensive gastric mucosal atrophy may decrease colonization by *H. pylori* and produce a low UBT value (19,20). Recent study has shown the UBT values are influenced by *H. pylori* colonization and neutrophil activity, and that these values are especially correlated with the severity of atrophic gastritis (21). However, Indonesia is a low *H. pylori* country (22). Therefore, urease-producing bacteria may allow roles other than *H. pylori* that cause chronic gastritis in Indonesia. Non *H. pylori* bacteria such as *Helicobacter spp., Mycobacterium spp.* and *Staphylococcus spp.* could produce urease enzyme (23).

Sufficient sensitivity and low specificity as a result of ^{14}C-UBT measured, showing that ^{14}C-UBT has sufficient ability to measure gastritis, but low specificity indicates a screening test was not good in classifying the disease severity of a person (24,25). Thus, other non-invasive modalities are needed to measure the severity of gastritis. The potential of serum pepsinogen was investigated as a noninvasive methods screening strategy for early stages of stomach cancer. Serum pepsinogen was introduced for severity gastritis of individuals. Pepsinogen serum test has the best cut-off values for diagnosing severity gastritis using serum PG I and PG I/PG II levels were found to be <25 ng/ml for PG I and <3.0 for PG I /

PG II. The corresponding specificity, sensitivity, positive predictive value, negative predictive value, and correctness rate were 98%, 82%, 0.97, 0.98 and 0.90, respectively. The same optimal cut-off values were identified for the patients with atrophic gastritis, with the specificity, sensitivity, positive predictive value, negative predictive value, and correctness rate of 100%, 90%, 1.00, 1.00 and 0.68, respectively. The high of sensitifity measured showed that serum pepsinogen was the best noninvasive methods fo severity gastritis (26).

Urease exposure can cause an inflammatory reaction by producing reactive oxygen species and inducing the expression of inducible NO-synthesizing enzyme (27). Urease can also give a toxic effect indirectly by producing ammonia, a product of urea hydrolysis (18). 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, namely IL-1, IL-8 and TNF-α (28). 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. Previous study prove that (29).

Based on demographic characteristics, Aged group >60 years old had a higher acute gastritis than other aged groups because ageing reduction in the number of mucous cells in the gastric mucosa of elderly associated with a decreasing prostaglandin concentration (22). The research finding also stated smokers had higher prevalence of acute gastritis than non smokers, and it had agreement with other studies (5). Smokers have higher cases in gastritis because gaster produce higher acid than non smokers. Female patients were higher proportion

suffered chronic and arophic gastritis, but it is insignificant. Some authors support a small contribution of sex differences that the male predominance in *H. pylori* related outcomes, including gastric cancer.

Conclusions

^{14}C-UBT is sufficient for predicting acute or chronic gastritis but not for atrophic gastritis.

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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)
Aged				
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

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

Table 4. Corelation analysis in 14-C UBT with acute, chronic, atrophic gastritis and intestinal metaplasia

Diagnosis	14-C Urea Breat Tes		P Value	r
	Positif	*Negatif*		
Acute Gastritis	9 (9.5)	86 (90.5)	P = 0.001	0.353
Chronic Gastritis	19 (20.0)	76 (80.0)	P = 0.000	0.433
Atrophy Gastritis	24 (25.3)	71 (74.7)	P = 0.038	0.213
Intestinal Metaplasia	2 (2.1)	93 (97.9)	P = 0.180	0.138

FIGURE

Figure Legends

Figure 1. ROC Curve of Acute Gastritis

Figure 2. ROC Curve of Chronic Gastritis

Figure 3. ROC Curve of Atrophic Gastritis

Figure 1

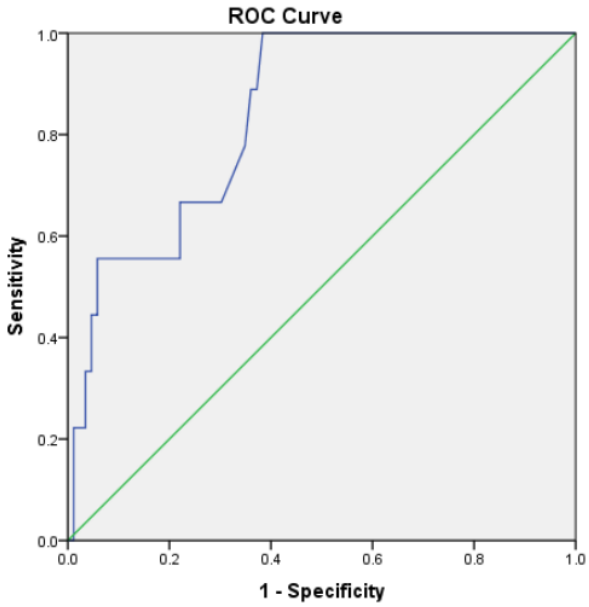

ROC Curve
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0
Diagonal segments are produced by ties.

Figure 2

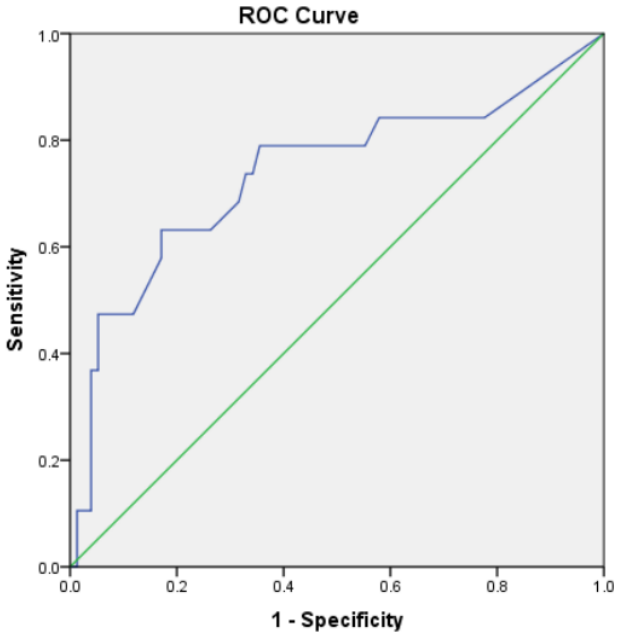
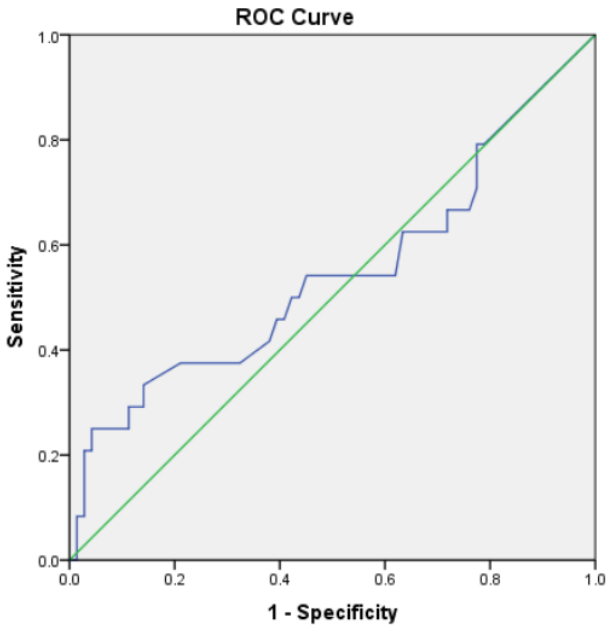

ROC Curve
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0
Diagonal segments are produced by ties.

Figure 3


ROC Curve
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0
Diagonal segments are produced by ties.

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