ORIGINAL PAPER

doi: 10.5455/medarh.2022.76.368-372
MED ARCH. 2022 OCT; 76(5): 368-372
RECEIVED: SEP 04, 2022
ACCEPTED: OCT 10, 2022

[1]Department of Clinical Pathology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

[2]Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

Corresponding author: Jelita Siregar. Department of Clinical Pathology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia. E-mail: jelita@gmail.com. ORCID ID: http//www.orcid.org/0000-0002-6054-913X.:

© 2022 Jelita Siregar, Darmadi Darmadi, Ratna Akbari Ganie

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Association Between Serum Midkine Level and Gastric Precancerous Lesion in Patients with Gastritis

Jelita Siregar[1], Darmadi Darmadi[2], Ratna Akbari Ganie[1]

ABSTRACT

Background: Gastric cancer is the fifth most common malignancy and the third highest cancer-related mortality worldwide after lung and colorectal cancers. The gastric carcinogenesis is started with precancerous lesion. Prompt diagnosis and management of gastric precancerous lesion may prevent disease progression. Midkine is a growth factor associated with various cancers and proposed as a marker for detecting gastric precancerous lesion. **Objective:** The aim of the study is to determine the association between serum midkine level and gastric precancerous lesion in patients with gastritis. **Methods:** A cross sectional study was conducted at Haji Adam Malik general hospital. Subjects were obtained by consecutive sampling. Inclusion criteria were patients aged 18 years or older, diagnosed with gastritis from gastroscopy and histopathology results, and willing to cooperate in the study. Each subjects underwent interview and endoscopic examination. Serum midkine level was determined using enzyme-linked immunosorbent assay (ELISA) method. Chi square, receiver operating characteristic (ROC) curve, and logistic regression tests were applied. **Results:** A total of 160 subjects were enrolled with 29.4% had gastric precancerous lesion. Serum midkine level was associated with gastric premalignant lesion. Cut off point for serum midkine level was 252 pg/mL with area under the curve of 0.816 ($p<0.001$). It's sensitivity, specificity, and accuracy in diagnosing gastric precancerous lesion were 74.5%, 71.7%, and 72.5%, respectively. Helicobacter pylori infection, high serum midkine level, heavy alcohol drinker, and family history of gastric cancer were risk factors for gastric precancerous lesion. **Conclusion:** Serum midkine level is associated with gastric premalignant lesion in patients with gastritis and has good diagnostic values.

Keywords: diagnostic, gastric, midkine, precancerous, risk.

1. BACKGROUND

Gastric cancer is the fifth most common malignancy and the third highest cancer-related mortality worldwide after lung and colorectal cancers (1, 2). The gastric carcinogenesis is a multifactorial process involving genetic susceptibility and environmental factors (2). Gastric precancerous lesion is a condition preceding gastric cancer which consists of chronic atrophic gastritis, metaplasia, foveolar hyperplasia, and gastric hyperplastic polyps (1, 2). The prevalence of gastric precancerous lesion is ranging from 3.2% to 19.8% (3). Up to 1 of 19 subjects with precancerous gastric lesion develops gastric cancer within 20 years (4). Early detection and management of gastric precancerous lesions may prevent progression to gastric cancer and reduce morbidity and mortality from the disease (1).

Midkine is a heparin-binding growth factor from a retinoic acid-responsive gene (5-7). It functions as modulator for proliferation and migration of various cells (6, 7). Rearrangement in the midkine coding gene results in elevated serum midkine level and ends in changing in cell cycle and malignancy, including gastric cancer cells (5-7). Midkine promotes gastric cancer cell survival and growth through activation of Akt and ERK1/2 pathways and upregulation of cell-cycle-related proteins such as cyclin A, cyclin D1, Cdk2, Cdk4, and Cdk6 (6). Serum midkine level may be a promising biomarker for detecting malignancies and disease progression after treatment (8). However, study regarding the role of serum midkine level in the incidence of gastric precancerous lesion is scarce. In this study, we aimed to determine the association between serum midkine level and gastric precancerous lesion in

patients with gastritis. Additionally, we also determined the diagnostic value of serum midkine level in detecting gastric precancerous lesion and risk factors for gastric precancerous lesion.

2. OBJECTIVE

The aim of this study is to determine the association between serum midkine level and gastric precancerous lesion in patients with gastritis.

3. MATERIAL AND METHODS

This was a cross sectional study conducted at Haji Adam Malik general hospital Medan, Indonesia. Subjects were obtained by consecutive sampling method. Inclusion criteria were patients aged 18 years or older, diagnosed with gastritis from gastroscopy and histopathology results, and willing to cooperate in the study. Exclusion criteria were patients receiving H. pylori eradication therapy within the last six months, taking antibiotics commonly used in H. pylori eradication regiment, consuming proton pump inhibitors and H2 receptor antagonists for the last one month, diagnosed with systemic diseases or malignancies, and pregnant women.

Each subject underwent interview to obtain demographic and health-related data. Smoking habit was measured using Brinkman index with a formula: mean amount of cigarettes consumed daily multiplied by smoking duration in year. Subjects then grouped into mild smoker (0-199) moderate smoker (200-599), and heavy smoker (>600). Alcohol consumption was measured using a formula: amount of alcohol consumed daily multiplied by drinking duration in year. Alcohol beverages measured including branded or traditional alcohol beverages. Subjects were grouped into non-drinker, mild to moderate drinker (<24 gram-year), and heavy drinker (>24 gram-year). Measuring unit for 10 grams ethanol were a glass/small bottle/can (285-330 mL) of beer, 30 mL of whiskey, and 120 mL of wine. Family history of gastric cancer was determined positive if there was a first-degree family member who had gastric cancer. Subject was categorized as overweight if body mass index was $\geq$23 kg/m^2.

Endoscopy was conducted to examine gastric mucosa. Characteristics of mucosa were determined including edema, erythema (spotted, patchy, linear), exudate, bleeding, and erosion. Mucosal biopsies were obtained for histopathology examination. Biopsies were obtained from five locations: major curvature (A1), minor distal antrum (A2), incisura angularis of minor curvature (A3), anterior wall of proximal corpus (C1), and posterior wall of proximal corpus (C2). Biopsies were also obtained from suspicious locations other than the above mentioned. Patients were diagnosed with gastric precancerous lesions if they had one of the following from histopathology examination: chronic atrophic gastritis, intestinal metaplasia, or dysplasia. Helicobacter pylori infection diagnosis was established from positive results of carbon-14 urea breath test (14C-UBT) and/or rapid urease test (Pronto Dry, France). Serum midkine level was determined using Human Midkine ELISA kit (Aviscera Bioscience Inc. CA, USA) from peripheral blood sample.

Characteristics	n (%)
Gender	
Male	86 (53.8)
Female	74 (46.3)
Age	
≥50 years	84 (52.5)
<50 years	76 (47.5)
Education	
Low	34 (21.3)
High	126 (78.8)
Ethnicity	
Batak	91 (56.9)
Non-Batak	69 (43.1)
Overweight	
Yes	59 (36.9)
No	101 (63.1)
Alcohol consumption	
Heavy drinker	25 (15.6)
Non- and mild to moderate drinker	135 (84.4)
Smoking	
Moderate and heavy smoker	65 (40.6)
Non- and mild smoker	95 (59.4)
Family history of gastric cancer	
Yes	7 (4.4)
No	153 (95.6)
H. pylori infection	
Yes	86 (53.8)
No	74 (46.3)
Gastric precancerous lesion	
Yes	47 (29.4)
No	113 (70.6)

Table 1. Characteristic of subject

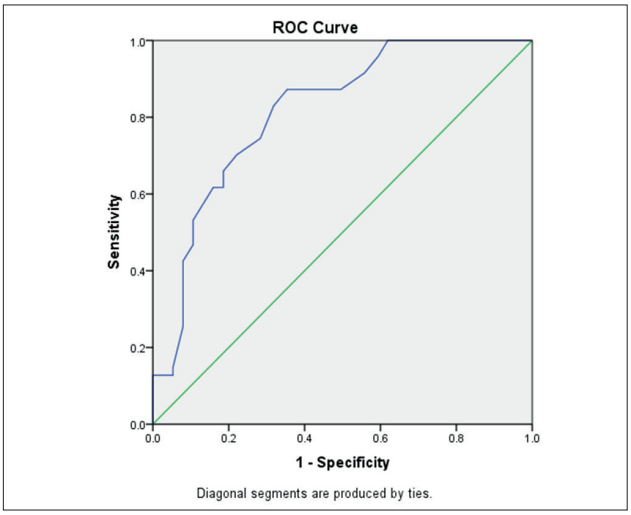

Figure 1. Receiver operating caracteristic curve of midkine in determining gastric precancerous lesion

Qualitative data was presented in frequency and percentage while quantitative data undergo normality test. Normally-distributed data was presented in mean and standard deviation but non-normally-distributed one was presented in median and minimum-maximum value. Chi square test was utilized to determine the association between qualitative data. Receiver operating

characteristic curve was used to determine the cut off point of serum midkine level in diagnosing gastric precancerous lesion. Diagnostic values were determined using the obtained cut off point. Logistic regression test was used to determine the risk factors for gastric precancerous lesion. All statistical analyses were done with 95% confidence interval and a p-value of <0.05 was considered significant. Statistical Package for the Social Sciences software was utilized to support the analysis. This study had been approved by Ethical Committee of Medical Faculty of Universitas Sumatera Utara.

4. RESULTS

A total of 160 subjects were enrolled in this study. Subjects were dominated by males, aged 50 years or older, with higher education level, with history of gastric cancer, and with H. pylori infection. Most subjects were not overweight, did not drink or only mild to moderately drink alcohol, did not smoke cigarette or only mild smoker, and without family history of gastric cancer. From our study, we found 29.4% subjects with gastric precancerous lesion (Table 1).

The median serum midkine level in our study was 240 pg/mL with a range of 65 to 400 pg/mL. We continued the analysis with receiver operating characteristic curve and found a cut off point of 252 pg/mL with area under the curve of 0.816 and a p-value of <0.001 (Figure 1). Subjects with serum midkine level below 252 pg/mL was categorized as low and vice versa. We used the cut off point to determine the diagnostic values of serum midkine level in diagnosing gastric precancerous lesion. The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ration, negative likelihood ratio, and accuracy were 74.5%, 71.7%, 52.2%, 87.1%, 2.63, 0.36, and 72.5%, respectively at serum midkine level of ≥252 pg/mL.

Bivariate analysis using chi square test showed that age, alcohol consumption, H. pylori infection, family history of gastric cancer, and high serum midkine level were associated with the incidence of gastric precancerous lesion. The prevalence ratio for each factor were 1.75, 1.85, 3.18, 2.6, and 4.05, respectively (Table 2).

All the five associated variables were involved in multivariate analysis. Of the all risk factors, only H. pylori infection, serum midkine level, alcohol consumption, and family history of gastric cancer which were related with incidence of gastric precancerous lesion if they present altogether. Infection of H. pylori and high serum midkine level had the highest relative risk (9.14 and 7.57, respectively) compared to subjects without infection and with low serum mudkine level (Table 3).

Risk factors	Gastric precancerous lesion	p	PR (95%CI)	
	Yes	No		
Gender Male Female	 30 (34.9%) 17 (23.0%)	 56 (65.1%) 57 (77.0%)	0.099	1.52 (0.91 – 2.52)
Age ≥50 years <50 years	 31 (36.9%) 16 (21.1%)	 53 (63.1%) 60 (78.9%)	0.028*	1.75 (1.05 – 2.94)
Education Low High	 12 (35.3%) 35 (27.8%)	 22 (64.7%) 91 (72.2%)	0.393	1.27 (0.74 – 2.17)
Ethnicity Batak Non-Batak	 31 (34.1%) 16 (23.2%)	 60 (65.9%) 53 (76.8%)	0.135	1.47 (0.88 – 2.46)
Overweight Yes No	 18 (30.5%) 29 (28.7%)	 41 (69.5%) 72 (71.3%)	0.810	1.06 (0.65 – 1.74)
Alcohol consumption Heavy drinker Non- and mild to moderate drinker	 12 (48.0%) 35 (25.9%)	 13 (52.0%) 100 (74.1%)	0.026*	1.85 (1.13 – 3.05)
Smoking Moderate and heavy smoker Non- and mild smoker	 15 (23.1%) 32 (33.7%)	 50 (76.9%) 63 (66.3%)	0.148	0.69 (0.41 – 1.16)
H. pylori infection Yes No	 37 (43.0%) 10 (13.5%)	 49 (57.0%) 64 (86.5%)	<0.001*	3.18 (1.7 – 5.95)
Family history of gastric cancer Yes No	 5 (71.4%) 42 (27.5%)	 2 (28.6%) 111 (72.5%)	0.024*	2.6 (1.52 – 4.44)
Serum midkine level High Low	280 (180 – 400) 35 (52.2%) 12 (12.9%)	204 (65 – 318) 32 (47.8%) 81 (87.1%)	< 0.001* < 0.001*	NA 4.05 (2.28 – 7.2)

Table 2. Bivariate analysis of risk factors for gastric precancerous lesion. *p<0.05; PR prevalence ratio; CI confidence interval

Risk factors	p	RR (95%CI)
H. pylori infection	<0.001*	9.14 (3.46 – 18.75)
High serum midkine level	0.002*	7.57(2.6 – 16.45)
Heavy alcohol drinker	0.011*	4.05 (1.92 – 11.06)
Family history of gastric cancer	0.046*	4.0 (1.80 – 9.37)
Age ≥50 years	0.250	2.58 (0.89 – 6.65)

Table 3. Multivariate analysis of risk factors for gastric precancerous lesion. RR relative risk; CI confidence interval

5. DISCUSSION

Gastric precancerous lesion is more frequent in males compared to females. Huang et al. reported that 62% of subjects with gastric precancerous lesion were males (9). Rentien et al. also reported similar result (10). However, Gu et al. found that females are dominating subjects with gastric precancerous lesion in China (11). A study from Italy by Dore et al. had similar result with previous study

(12). Song et al. found a slightly higher female domination in their study (4). Mean age of subjects with gastric precancerous lesion was reported to be 57.5 years (9). In a study from China, the mean age was 51.63 years (11). In Sweden, the mean age for subjects with this condition was 56 years. Advanced lesion was observed in line with advanced age (4). The abovementioned results were supported by Adjarkosh et al. They reported a mean age of 57.87 years (3). In this study, males were dominating the proportion of subjects with gastric precancerous lesion. Subjects aged 50 years or older were also tend to suffer from gastric precancerous lesion compared to their counterparts.

Education level was reported to be associated with the incidence of gastric precancerous lesion. The higher the education level, the higher the risk of gastric precancerous lesion. Body mass index had no significant relationship with gastric precancerous lesion. According to a study, body mass index of subjects with the condition was 23.51 kg/m^2. Regarding alcohol consumption, a study from China declined its association with gastric precancerous lesion. More than 90% of subjects with the disease did not consume alcohol. Similar with alcohol consumption, smoking was not significantly associated with gastric precancerous lesion. The proportion of subjects with such condition who smoke cigarette was lower than 25% (11). There is no specific publication discussing the role of ethnicity in the incidence of gastric precancerous lesion. In our study, subjects with gastric precancerous lesion tended to have higher education and were non- or only mild smoker. Both were not associated with the incidence of gastric precancerous lesion. Majority subjects with the lesion were non- or mild to moderate alcohol drinker. We found significant association between alcohol consumption and gastric precancerous lesion. Similar with previous study, majority subjects with lesion in this study were not overweight but there was a significant association between overweight and the incidence of gastric precancerous lesion.

Genetic predisposition plays important role in the progression of gastric cancer. Family history of gastric cancer increases the risk for gastric precancerous lesion and H. pylori infection (13). Other conditions such as gastric lymphoma, atrophic gastritis, and intestinal metaplasia and dysplasia are also associated with the risk of gastric precancerous lesion. The lesion still can be detected even if the previous conditions have been eliminated (10). However, there is a study confronting previous results. They found that only 15.41% of subjects with gastric precancerous lesion who have family history of malignant diseases (11). Similar with the last study, dominant subjects with gastric precancerous lesion in our study did not have family history of gastric cancer. But in contrast, we found significant association between family history of gastric cancer and the incidence of gastric precancerous lesion.

Several tumor markers have been studied and proposed to aid in detecting progressivity of precancerous lesion into malignancy in stomach. Jeong et al. in their study reported that mitochondrial microsatellite instability (mtMSI) can be utilized as a marker of progressivity of gastric malignancy especially intestinal type. The presence of mtMSI in patients with gastric dysplasia will increase the risk for developing into gastric cancer (14). Other markers include cytokines produced by T-helper 2 (Th2) cells. Elevation of CCL3/MIP1A, CCL20/MIP3A, interleukin (IL)-1β, IL-4, and IL-5 increase the risk of gastric precancerous development with odds ratios of 2.69, 2.39, 3.02, and 3.07, respectively compared to the counterparts (15). Aridome et al. found that midkine is associated with the incidence of malignancy in digestive tract. Changing in midkine coding gene was absent in non-malignant group, but present in 12 of 16 subject with gastric cancer, in 8 of 13 subjects with colorectal cancer, in five of nine subjects with hepatocellular carcinoma, and in all subjects with esophageal and duodenal ampulla cancers. Midkine was also detected in all subjects with lymph node metastasis (5). Midkine also plays important role in diagnosing squamous cell carcinomas in head and neck region. Midkine can be utilized to monitor therapeutic response too. A study by Yamashita et al. found a positive correlation between serum midkine level and immunohistochemistry scoring with sensitivity and specificity of 57.3% and 85.3%, respectively at 482 pg/mL. Decreased serum midkine level was also associated with therapeutic response, especially chemotherapy. High serum midkine level was in line with unfavorable outcome (8).

Elevated serum midkine level is also observed in patients with gastroesophageal cancer along with elevated serum IL-1, IL-6, IL-8, TNF-alpha, VEGF-A, and VEGF-C. Serum midkine level is associated with cancer staging and symptom such as weight loss (16). Xu et al. in their study found that midkine expression in gastric cancer cell is elevated compared to normal gastric cell. Midkine knockdown resulted in decreased gastric cancer cell proliferation and inhibition cancer progressivity (6). Huang et al. conducted a study in subjects with gastric cancer. They reported that serum and urine midkine level are elevated in the study subjects. Further analysis using polymerase chain reaction method showed that midkine coding gene expression is higher in advanced cancer tissue. In contrast, this finding was not associated with tumor differentiation and size and lymph node involvement (7). In our study, there were significant difference in serum midkine level in subjects with gastric precancerous lesion and their counterparts. Higher serum midkine level was observed in subjects with gastric precancerous lesion and increased the risk for corresponding condition as high as 4.05 times. With a cut off point of 252 pg/mL, serum midkine level might predict the incidence of gastric precancerous lesion at 74.5% sensitivity, 71.7% specificity, and 72.5% accuracy.

A study by Zhou et al. identified risk factors for gastric precancerous lesion. Advanced age increased the risk at 1.027 times compared to younger age. Male and smoker were also risk factors with odds ratios of 1.303 and 1.142, respectively. Other significant risk factors were H. pylori infection and pepsinogen I level (odds ratios of 1.377 and 1.536, respectively). Diet consisted of high fat had

protective effect with odds ratio of 0.731 (17). Ajdarkosh et al. supported the previous results. They found that age and H. pylori infection are significantly affect the incidence of gastric precancerous lesion. Advanced age increased the risk as high as 3.1 times while H. pylori infection increased the risk as high as 3.56 times (3). Another study from Italy reported that H. pylori infection is significantly associated with increased risk for gastric precancerous lesion. In contrast, age and gender did not have significant association with the condition (9). Bile reflux was another risk factor for gastric precancerous lesion. After excluding other confounding factors such as gender and age, bile reflux was still significantly associated with gastric precancerous lesion. Bile reflux itself was positively correlated with severity of gastric lesion (18). Logistic regression analysis in our study showed that H. pylori infection, high serum midkine level, heavy alcohol drinker, and family history of gastric cancer are risk factors for gastric precancerous lesion. The strongest risk factor was H. pylori infection (OR 9.14) followed by high serum midkine level (OR 7.57).

Our study was the first study determining the association between serum midkine level and gastric premalignant lesion. We suggest to use serum midkine level to aid in diagnosing gastric premalignant lesion in patients with gastritis. However, we did not include healthy subjects as controls. Therefore, further study enrolling healthy subjects as controls is mandatory to determine the role of serum midkine level in diagnosing gastric premalignant lesion in general population.

6. CONCLUSION

Serum midkine level is associated with gastric premalignant lesion in patients with gastritis. Serum midkine level has good diagnostic values. Other risk factors for gastric premalignant lesion are H. pylori infection, heavy alcohol drinker, and family history of gastric cancer.

REFERENCES

1. Yang H, Yang W, Hu B. Gastric epithelial histology and precancerous conditions. World J Gastrointest Oncol. 2022; 14: 396-412. DOI: https://doi.org/10.4251%2Fwjgo.v14.i2.396.
2. Gullo I, Grillo F, Mastracci L, Vanoli A, Carneiro F, Saragoni L, et al. Precancerous lesions of the stomach, gastric cancer and hereditary gastric cancer syndromes. Pathologica. 2020; 112: 166-185. DOI: https://doi.org/10.32074%2F1591-951X-166.
3. Ajdarkosh H, Sohrabi M, Moradniani M, Rakhshani N, Sotodeh M, Hemmasi G, et al. Prevalence of gastric precancerous lesions among chronic dyspeptic patients and related common risk factors. Eur J Cancer Prev. 2015; 24: 400-406. DOI: https://doi.org/10.1097/cej.0000000000000118.
4. Song H, Ekheden IG, Zongli Z, Ericsson J, Nyren O, Ye W. Incidence of gastric cancer among patients with gastric precancerous lesions: observational cohort study in a low risk Western population. BMJ. 2015; 351: h3867. DOI: https://doi.org/10.1136%2Fbmj.h3867.
5. Aridome K, Takao S, Kaname T, Kadomatsu K, Natsugoe S, Kijima F, et al. Truncated midkine as a marker of diagnosis and detection of nodal metastases in gastrointestinal carcinomas. Br J Cancer. 1988; 78: 472-477. DOI: https://doi.org/10.1038%2Fbjc.1998.517.
6. Xu Y, Qu X, Zhang X, Luo Y, Zhang Y, Luo Y, et al. Midkine positively regulates the proliferation of human gastric cancer cells. Cancer Lett. 2009; 279: 137-144. DOI: https://doi.org/10.1016/j.canlet.2009.01.024.
7. Huang Y, Cao G, Wang H, Wang Q, Hou Y. The expression and location of midkine in gastric carcinomas of Chinese patients. Cell Mol Immunol. 2007; 4: 135-140. PMID: 17484808.
8. Yamashita T, Shimada H, Tanaka S, Araki K, Tomifuji M, Mizokami D, et al. Serum midkine as a biomarker for malignancy, prognosis, and chemosensitivity in head and neck squamous cell carcinoma. Cancer Med. 2016; 5: 415-425. DOI: https://doi.org/10.1002/cam4.600.
9. Huang S, Guo Y, Li Z, Shui G, Tian H, Li B, et al. Identification and validation of plasma metabolomic signatures in precancerous gastric lesions that progress to cancer. JAMA Netw Open. 2021; 4: e2114186. DOI: https://doi.org/10.1001/jamanetworkopen.2021.14186.
10. Rentien A, Levy M, Copie-Bergman C, Gagniere C, Dupuis J, Baleur YL, et al. Long-term course of precancerous lesions arising in patients with gastric MALT lymphoma. Dig Liver Dis. 2018; 50: 181-188. DOI: https://doi.org/10.1016/j.dld.2017.10.014.
11. Gu J, Xie S, Wang S, Xue L, Zhou J, Li M, et al. Surveillance of premalignant gastric cardia lesions: a population-based prospective cohort study in China. Int J Cancer. 2021; 149: 1639-1648. DOI: https://doi.org/10.1002/ijc.33720.
12. Dore MP, Cipolli A, Ruggiu MW, Manca A, Bassotti G, Pes GM. Helicobacter pylori eradication may influence timing of endoscopic surveillance for gastric cancer in patients with gastric precancerous lesions: a retrospective study. Medicine (Baltimore). 2018; 97: e9734. DOI: https://doi.org/10.1097/md.0000000000009734.
13. Motta CRA, Cunha MPSS, Queiroz DMM, Cruz FWS, Guerra EJC, Mota RMS, et al. Gastric precancerous lesions and helicobacter pylori infection in relatives of gastric cancer patients from Northeastern Brazil. Digestion. 2008; 78: 3-8. DOI: https://doi.org/10.1159/000151297.
14. Jeong C, Lee J, Sohn S, Ryu S, Kim D. Mitochondrial microsatellite instability in gastric cancer and gastric epithelial dysplasia as a precancerous lesion. Cancer Epidemiol. 2010; 34: 232-237. DOI: https://doi.org/10.1016/j.canep.2010.03.015.
15. Song M, Rabkin CS, Torres J, Kemp TJ, Zabaleta J, Pinto LA, et al. Circulating inflammation-related markers and advanced gastric premalignant lesions. J Gastroenterol Hepatol. 2019; 34: 852-856. DOI: https://doi.org/10.1111/jgh.14518.
16. Krzystek-Korpacka M, Matusiewicz M, Diakowska D, Grabowski K, Blachut K, Kustrzeba-Wojcicka I, et al. Impact of weight loss on circulationg IL-1, IL-6, IL-8, TNF-alpha, VEGF-A, VEGF-C and midkine in gastroesophageal cancer patients. Clin Biochem. 2007; 40: 1353-1360. DOI: https://doi.org/10.1016/j.clinbiochem.2007.07.013.
17. Zhou X, Zhu H, Zhu C, Lin K, Cai Q, Li Z, et al. Helicobacter pylori infecyion and serum pepsinogen level with the risk of gastric precancerous conditions: a cross-sectional study of high-risk gastric cancer population in China. J Clin Gastroenterol. 2021; 55: 778-784. DOI: https://doi.org/10.1097/mcg.0000000000001444.
18. Li D, Zhang J, Yao WY, Zhang DL, Feng CC, He Q, et al. The relationship between gastric cancer, its precancerous lesions and bile reflux: a retrospective study. J Dig Dis. 2020; 21: 222-229. DOI: https://doi.org/10.1111/1751-2980.12858.