RESEARCH ARTICLE

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Determining Gastric Cancer-Related Risk Factors in Mongolian Population Using ABC(D) Method: A Matched Case-Control Study

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Abstract

Objective: We aimed to identify gastric cancer-related risk factors and evaluate the efficacy of screening ABC(D) method in determining high risk gastric cancer individuals in Mongolian population. **Methods:** A total of 240 participants (120 gastric cancer patients and 120 healthy individuals) were included in this study. Data were collecting using a structured questionnaire consisting of 56 questions covering 5 categories. Serum *Helicobacter pylori* IgG (*H. pylori* IgG), pepsinogen I (PGI), and pepsinogen II (PGII) were tested in one third of all the participants (40 gastric cancer patients and 40 controls). PGI, PGII, and *H. pylori* IgG levels were measured using GastroPanel enzyme-linked immunosorbent assay kit (Biohit, Helsinki, Finland). **Results:** Habits of having leftover meals (OR 2.22, 95%CI 1.27-3.86, p<0.01), daily consumption of tea with salt (OR 1.97, 95%CI 1.18-3.30, p<0.01), smoking on an empty stomach (OR 2.44, 95%CI 1.11-5.37, p<0.05), daily consumption of vegetables (OR 0.45, 95%CI 0.27-0.76, p<0.01), and daily consumption of fruit juice (OR 0.36, 95%CI 0.15-0.85, p<0.05), family history of gastric cancer (parents OR 2.88, 95%CI 1.07-7.78, p<0.05, siblings (OR 3.09, 95%CI 1.09-8.81, p<0.05), and history of gastric diseases (OR 3.65, 95%CI 2.10-6.35, p<0.0001) were identified as protective factors. A low PGI level (<35.25ng/ml) and low PGI/II ratio (<4) were associated with gastric cancer risk. According to ABC(D) method, groups C and D had higher proportion of gastric cancer cases than group A and B (group C, OR 7.50, 95%CI 1.20-47.05, p<0.05; group D, OR 8.3, 95%CI 1.33-51.26, p<0.05). **Conclusion:** Our findings suggested that gastric cancer risk was more closely related to eating habits, smoking, family history, and precancerous lesions. ABC(D) method seems to be a plausible alternative or supplementary method for stratifying patients at high risk of gastric cancer in this country.

Keywords: ABC(D) method- cancer risk- *H. pylori*- pepsinogen- screening cancer

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Introduction

The incidence of gastric cancer has been declining worldwide in recent years; on the contrary, it has increased in the last decade in Mongolia (Lonjid et al., 2020). According to International Agency for Research on Cancer, Mongolia had the highest rate of gastric cancer(32.5 new cases per 100,000 population), followed by Japan (100,000:31.6), and South Korea (100,000:27.9) for both sexes in 2020. In addition, Mongolia has the highest mortality rate for gastric cancer(100,000:24.6), while Japan (100,000:8.2) and South Korea (100,000:8.2) ranked 34 and 56, respectively (WHO, 2020). There are many risk factors for gastric cancer aside from *H. pylori* infection, which is the most common cause of gastric cancer (Gantuya et al., 2018; Song et al., 2015; Lou et al., 2020; Chen et al., 2013; Ladeiras-Lopez et al., 2008; Choi and Kim, 2016; Rahman and Cao, 2016). WHO has stated that 30-50% of cancer deaths can be prevented by avoiding some risk factors, such as alcohol and tobacco consumption, and maintaining a healthy weight and exercising regularly (WHO, 2020). Early detection of gastric cancer can also reduce gastric cancer-related deaths by 30-65% (Hamashima et al., 2013). Different population-based screening strategies are currently being adopted successfully in Korea, Japan, and high incidence regions of China and Taiwan to reduce gastric cancer morbidity and mortality (Baek et al., 2020). Unfortunately,

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a screening program has not been introduced yet for gastric cancer, consequently over 80% of gastric cancer cases are diagnosed in the late stage in our country (Center of Health Development, Mongolia, 2019). Currently, a gastroduodenoscopy and histological evaluation is done to diagnose gastric cancer. These methods are an effective diagnostic modality for gastric diseases, but they invasive and uncomfortable for the patients. Therefore, there is an urgent need to introduce effective screening method to stratify high risk-population to decrease gastric cancer incidence and mortality in this country. In some wealthy countries, such as Japan, South Korea, China, Finland, and Brazil, *H. pylori* IgG, PGI, and PGI/II ratios have been started to be used as a non-invasive serological evaluation of gastric cancer (Tu et al., 2017; Mattar et al., 2020; Chapelle et al., 2020; Yoshida et al., 2014). Human pepsinogens, which are protein-digestive enzymes secreted as proenzymes by chief cells, are classified into PGI and PGII. The serum PGI level and PGI/II ratio have been used as markers for screening individuals at high risk of gastric cancer or diagnosing gastric cancer and precancerous lesions (Tu et al., 2017; Miki, 2011). Miki (2011), who is a Japanese researcher, developed ABC(D) method which is combination of *H. pylori* IgG and PGs (PGI<70ng/ml and PGI/II ratio<3.0 as positive PGs). To stratify high risk patients of gastric cancer, Miki divided participants into four groups as follows: group A, *H. pylori*(-), PGs(-); group B, *H. pylori*(+), PGs(-); group C *H. pylori*(+), PGs(+); group D, *H. pylori*(-), PGs(+) for atrophic marker (Miki, 2011). In this study, we aimed to identify gastric cancer-related risk factors and evaluate the use of ABC(D) screening method to determine high risk-population for gastric cancer in Mongolian individuals.

Materials and Methods

Study population

This hospital based case-control study was conducted from November 2017 to February 2020. For this purpose, we selected 120 newly diagnosed patients from National Cancer Center of Mongolia before undergoing surgery and other therapies. The patients' diagnosis was confirmed based on the gastroduodenoscopy and histological examination by one expert. Besides, we enrolled 120 healthy individuals as controls. The controls did not have any obvious disease based on their complete blood count, urinalysis, and biochemical profile. Participants of two groups were matched by age (±2), sex, and ethnicity. Exclusion criteria were as follows: age <18, pregnancy, recent use of proton pump inhibitor or histamine-2 receptor blockers, history of *H. pylori* eradication within previous three months, and history of gastric surgery or other cancers. Written informed consent was obtained from all 240 participants.

Identification of gastric cancer-related risk factors

All patients and controls were personally interviewed by trained researchers. We modified the questionnaire of Mongolian Steps Survey on the Prevalence of Noncommunicable Disease Risk Factors. A structured questionnaire consisting of 56 questions covering 5 categories was used for data collection. The questionnaire included following categories: (1) demographic factors, including age, sex, ethnicity, education, income, height, weight, and blood type, (2) dietary habit factors, including some eating habits, consumption of salt, spicy foods, vinegar and ketchup, and consumption of moldy foods etc., (3) dietary intake, including 21 foods and beverages, (4) smoking and alcohol intake, and (5) family history of gastric cancer and previous history of gastric disease.

Serum H. Pylori IgG and pepsinogens measurement

We selected one third of the participants (40 gastric cancer patients, 40 healthy controls) randomly and analyzed their serum *H. pylori* IgG, PGI, and PGII. PGI, PGII, and *H. pylori* IgG levels were measured using GastroPanel enzyme-linked immunosorbent assay kit (Biohit, Helsinki, Finland). To obtain more accurate results, the concentration of serum markers was used for the average value of the results of a triplicate analysis repeated twice. Fasting blood samples of all the participants were collected and kept in EDTA tubes. The blood samples were centrifuged at 2000rpm for 10 minutes, and the supernatant was stored at -70°C freezer until testing. Before the assay, the samples were diluted with diluent buffer according to kit instruction: 1:20 for PGI and PGII, and 1:400 for *H. pylori* IgG. The serum concentrations of PGI, PGII, and *H. pylori* IgG were tested according to the manufacturer's instructions. The absorbance of the microplate wells was measured at 450 nm using BIOBASE-EL10A microplate reader (Biobase Biodustry, Shandong, China). In addition, PGI/II ratio was calculated.

Statistical analysis

All statistical analyses were performed by SPSS (version 26.0, Chicago, IL, USA). Categorical variables were presented as numbers and proportions and differences were assessed using Chi-square test. Univariate analysis and multivariate logistic regression analysis were performed and odds ratio (OR) and 95% confidence intervals (95%CI) were expressed to evaluate relationship between risk factors and gastric cancer. Mean value and standard deviation of continuous variables were calculated. The continuous variables were compared by Student's T test. Differences with $p<0.05$ were considered to be statistically significant.

Results

Demographic characteristics

The mean age of the participants was 59.2±11.4 (ranged 26-85) years old. About 61.7% (n=148) of the participants were male. Geographically, 43.2%, 19.1%, 19.1%, 11.2%, and 7.5% were residents of Ulaanbaatar city, Western, Khangai, Central, and Eastern region, respectively. Demographic characteristics of the study participants are shown in Table 1.

Gastric cancer-related risk factors

The results on dietary habits, dietary intake, and smoking, and alcohol intake variables are presented

Table1. Demographic Characteristics of the Subjects

Characteristics	Healthy controls N (%)	Gastric cancer patients N (%)	p-value
Age (year, mean±SD)*	59.2±11.1	59.1±11.1	0.94
Sex (male)*	74 (61.7)	74 (61.7)	1
Ethnicity (khalkh)	99 (83.2)	95 (79.2)	0.426
Education (graduated)	62 (52.1)	55 (45.8)	0.332
Body mass index (mean, kg/m^2±SD)	26.9±4.9	25.6±4.9	0.147
Body mass index (>25)	21 (43.8)	9 (30.0)	0.225
Occupation (normal)	78 (67.8)	101 (84.2)	0.003
Monthly income, thousand MNT (mean±SD)	860.3±461.3	787.3±600.3	0.386
Blood type			0.828
0I,	35 (34.7),	36 (35.6),	
AII,	29 (28.7),	29 (28.7),	
BII,	31 (30.7),	27 (26.7),	
ABIV	6 (5.9)	9 (8.9)	

in Table 2. Regarding dietary habit, it was found that having dinner after 6.00pm (OR 1.42, 95%CI 1.11-1.83, p<0.01) and having leftover meals (OR 2.22, 95%CI 1.27-3.86, p<0.01) significantly increased gastric cancer risk. In contrast, eating at regular times (OR 0.43, 95%CI 0.25-0.73, p<0.01), chewing thoroughly (OR 0.39, 95%CI 0.23-0.67, p<0.01), and cooking meat completely (OR 0.48, 95%CI 0.25-0.97, p<0.05) significantly reduced gastric cancer risk based on our findings. The average salt intake of the total participants was 11.7±4.9g/day. About 48% of the healthy controls and 69% of the patients with gastric cancer consumed tea with salt every day, revealing salt intake relation with gastric cancer risk (OR 1.97, 95%CI 1.18-3.30, p<0.01). In terms of dietary intake, daily consumption of meat ≥400g (total daily amount for a family) (OR 0.57, 95% CI 0.35–0.91, p<0.01), daily

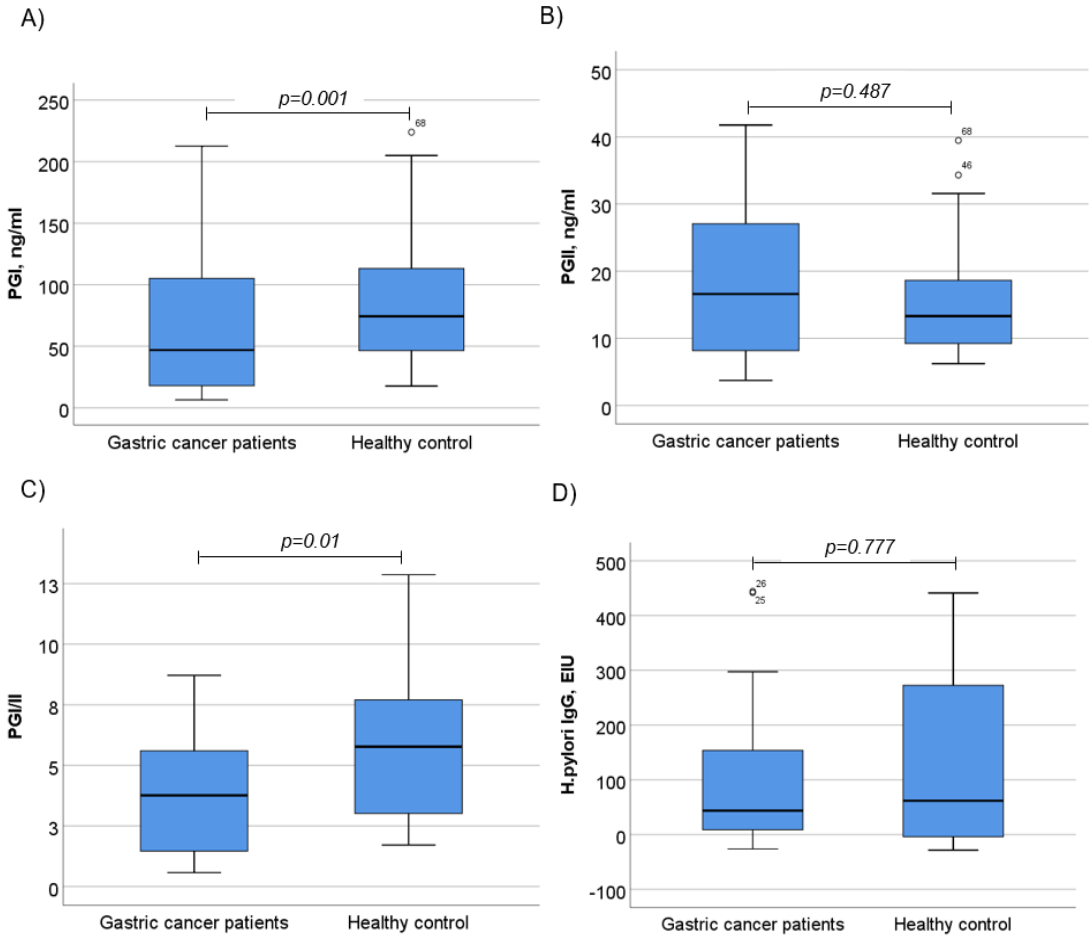

Figure 1. Serum PGI (A), PGII (B), PGI/II Ratio (C), and *H.pylori* IgG (D) Levels in the Study Groups

Table 2. Comparison of the Dietary Habits, Dietary Intake, and Smoking and Alcohol Intake between Study Groups

Variables	Healthy controls N (%)	Gastric cancer patients N (%)	OR (95% CI)
Dietary habit			
Eating at regular times (yes)	65 (54.2)	39 (33.6)	0.43 (0.25-0.73)
Having dinner after 6.00pm (yes)	80 (67.2)	98 (81.7)	1.42 (1.11-1.83)
Chewing thoroughly (yes)	88 (73.9)	63 (52.5)	0.39 (0.23-0.67)
Cooking meat thoroughly until it's tender (yes)	101 (86.3)	91 (75.8)	0.48 (0.25-0.97)
Eating or drinking hot drink and meal (yes)	78 (66.1)	73 (60.8)	0.80 (0.47-1.35)
Having left over meals (yes)	70 (58.3)	90 (75.6)	2.22 (1.27-3.86)
Moldy foods (yes)	19 (16.1)	16 (13.7)	0.83 (0.40-1.70)
Daily intake of salt (g, mean±SD)	12.4±4.7	11.0±5.0	-
Tea with salt (everyday)	48 (40.7)	69 (57.5)	1.97 (1.18-3.30)
Pickled and preserved foods (yes)	7 (6.0)	5 (4.3)	0.71 (0.22-2.32)
Spicy foods (yes)	54 (45.4)	53 (44.2)	1.05 (0.63-1.75)
Vinegar and ketchup (yes)	48 (41.4)	18 (36.0)	0.61 (0.63-2.49)
Dietary intake			
Beef or mutton (>400g, everyday)	104 (88.9)	89 (75.4)	0.57(0.35-0.91)
Beef or mutton (>600g, everyday)	31 (26.5)	44 (37.3)	1.3 (0.95-1.01)
Traditional air-dried meat /borts/ (every week)	8 (6.7)	12 (10.2)	1.57 (0.62-3.99)
Ham and smoked meat (every week)	4(3.4)	13 (10.8)	1.5 (1.17-2.13)
Fruits (everyday)	7 (5.8)	6 (5.1)	0.86 (0.28-2.63)
Vegetables (everyday)	70 (58.8)	46 (39.3)	0.45 (0.27-0.76)
Garlic (yes)	95 (79.8)	107 (89.2)	2.08 (1.00-4.31)
Whole grain, wheat flour and bran (>2 times in a week)	32 (27.1)	39 (33.3)	1.34 (0.77-2.35)
Buckwheat and pearl barley (>2 times in a week)	26 (22.2)	27 (23.1)	1.05 (0.57-1.94)
Milk or dairy product (>2 times in a week)	98 (82.4)	92 (78.6)	0.79 (0.41-1.50)
Traditional clarified butter /shar tos/ (yes)	19 (15.8)	27 (22.5)	0.65 (0.34-1.24)
Butter (yes)	8 (6.7)	14 (11.7)	1.35 (0.75-4.59)
Olive oil (yes)	17 (14.2)	10 (8.3)	0.55 (0.24-1.26)
Sunflower oil (yes)	100 (83.3)	96 (80.0)	0.80 (0.42-1.54)
Coffee (yes)	22 (18.3)	17 (14.2)	0.73 (0.37-1.47)
Tea with milk (everyday)	81 (67.5)	71 (59.2)	0.70 (0.41-1.18)
Black tea (everyday)	48 (40.0)	37 (30.8)	0.67 (0.39-1.14)
Green tea (everyday)	18 (15.0)	14 (11.7)	0.75 (0.35-1.58)
Boiled water (everyday)	39 (32.5)	25 (20.8)	0.55 (0.31-0.98)
Soda (everyday)	15 (12.5)	11 (9.2)	0.71 (0.31-1.61)
Smoking and alcohol			
Smoking (yes)	50 (41.6)	61 (50.8)	1.45 (0.87-2.41)
Passive smoking (yes)	16 (16.5)	28 (24.3)	0.61 (0.31-1.22)
Smoking on an empty stomach (yes)	16 (33.3)	33 (55.0)	2.44 (1.11-5.37)
Duration of smoking (year, mean±SD)	24.5±15.8	28±12.6	-
Alcohol intake in the last 12 months (yes)	65 (56.5)	72 (61.0)	0.83 (0.93-1.40)
Frequency of alcohol intake (every week)	9 (13.6)	7 (9.7)	(0.51-4.19) 1.47

consumption of vegetables (OR 0.45, 95% CI 0.27-0.76, p<0.01), and daily fruit juice intake (OR 0.36, 95%CI 0.15-0.85, p<0.05) were associated with a protective effect against this cancer. Whereas, it was observed that weekly consumption of ham and smoked meat (OR 1.5, 95% CI 1.17–2.13, p<0.05) and consumption of fat grease (OR 2.09, 95%CI 1.03-4.24, p<0.05) increased gastric cancer risk. Moreover, we found that smoking on an empty stomach increased gastric cancer risk (OR 2.44, 95%CI 1.11-5.37, p<0.05). Two groups were also compared in terms of history of gastric diseases and family history of gastric cancer. Gastric cancer history in first-degree relatives was significantly associated with gastric cancer risk; for father/mother (OR 2.88, 95%CI

Table 3. Risk Assessment of Gastric Cancer According to ABC(D) Method

Classification	Healthy controls N (%)	Gastric cancer patients N (%)	OR (CI 95%)
Group A	9 (25.7)	2 (7.1)	reference
Group B	14 (40)	5 (17.9)	1.61 (0.26-10.13)
Group C	6 (17.1)	10 (35.7)	7.50 (1.20-47.05)
Group D	6 (17.1)	11 (39.3)	8.25 (1.33-51.26)

1.07-7.78, p<0.05) and in siblings (OR 3.09, 95%CI 1.09-8.81, p<0.05). Furthermore, 58.8% of patients with gastric cancer had history of gastric diseases almost twice higher than those in healthy controls (28.1%), revealing highly significant odds ratio (OR 3.65, 95%CI 2.10-6.35, p<0.0001).

Determination of high risk-population by ABC(D) method

We selected a total of 80 participants (40 healthy controls and 40 patients with gastric cancer) randomly and tested their serum *H. pylori* IgG, PGI, and PGII. For the purpose of doing the analysis, histograms were made on each biomarker, the excessive deviations were subtracted, and the analysis was performed on 35 healthy controls and 28 patients with gastric cancer. The mean of serum PGI level was 68.11±35.39 ng/ml for the controls and 43.35±36.67 ng/ml for the gastric cancer patients (Figure 1A). The serum PGI level was significantly lower in patients with gastric cancer as compared to the controls (p<0.01). The mean of serum PGII level was 13.29±5.98 ng/ml and 14.94±10.44 for the controls and gastric cancer patients, respectively (Figure 1B). The mean of serum PGI/II ratio was 5.49±2.83 for controls and 3.40±2.56 for gastric cancer patients (Figure 1C). The PGI/II ratio was significantly lower in gastric cancer group compared with control group (p<0.01). There were no significant differences between study groups regarding serum *H. pylori* IgG status (Figure 1D). Corresponding receiver operating characteristics (ROC) curves of PGI and PGI/II ratio were developed for detecting gastric cancer, and area under the curves (AUC) were 65.2 (95%CI 53.0-77.3, p<0.05) and 62.7 (95%CI 50.1-75.3, p<0.05), respectively. When optimal cut-off value of PGI was ≤35.25ng/ml, the sensitivity and specificity were 60.7% and 80.0%, respectively. Moreover, when optimal cut-off value of PGI/II ratio was <4.0, the sensitivity and specificity were 67.8% and 65.7%, respectively. According to ABC(D) method, we classified participants into four groups[17]. We modified PGs criteria based our cut-off values (PGI<35.25ng/ml and PGI/II ratio<4.0 as positive PGs), and divided participants into four groupsof group A, *H. pylori*(-), PGs(-); group B, *H. pylori*(+), PGs(-); group C *H. pylori*(+), PGs(+); group D, *H. pylori*(-), PGs(+). According to the classification, 11 (17.5%) were categorized as group A, 19 (30.2%) as group B, 16 (25.3%) as group C, 17 (27.0%) as group D. Prevalence of gastric cancer was significantly different among all groups (p<0.05). Groups C and D had higher proportions of gastric cancer cases than group A and B (group C, OR 7.50, 95%CI 1.20-47.05, p<0.05; group D, OR 8.3, 95%CI 1.33-51.26, p<0.05) (Table 4).

Discussion

In this study, it was found that having dinner after 6.00pm, having leftover meals, weekly consumption of ham and smoked meat, consumption of fat grease, smoking on an empty stomach, history of previous gastric diseases, and family history of gastric cancer were associated with higher risk of developing gastric cancer. Similarly, previous studies have shown that smoked meat, smoking tobacco, family history of gastric cancer, and precancerous gastric lesions, and obesity are associated with higher risk of gastric cancer. However, a meta-analysis study has shown that overweight (RR 1.21, 95%CI 1.03-1.42) and obese status (RR 1.82, 95%CI 1.32-2.49) were positively related to cardia rather than non-cardia gastric cancer (Chen et al., 2013). In this study, body mass index was not associated with gastric cancer risk. This discrepancy in results of two studies can be attributed to this issue that most of the gastric cancers registered in Mongolia were diagnosed with non-cardia cancers. In this study, dietary salt intake did not lead to a significant difference between the two study groups. It should be noted that dietary salt intake among our participants was two-fold higher (11.7±4.9g/day) than the World Health Organization recommendation (<5g/day). However, previous studies revealed that excessive salt intake was strongly associated with gastric cancer risk (D'Elia et al., 2014; Goto et al., 2020; D'Elia et al., 2012). Interestingly, drinking tea with salt every day was identified as a significant risk factor for gastric cancer (OR 1.97, 95%CI 1.18-3.30, p=0.01). This finding can justify the high rate of gastric cancer incidence in Western region of Mongolia , in where the population has a habit of drinking tea with salt. In addition, based on our study findings, eating at regular times, chewing thoroughly, cooking meat thoroughly, daily consumption of meat ≥400g, daily consumption of vegetables, and daily fruit juice intake significantly reduced gastric cancer risk. All participants' daily consumption of fruits and vegetables was less than WHO recommendations. Only 5.1% and 5.8% of the participants in the gastric cancer and control groups, respectively, consumed fruit daily. However, two groups did not differ significantly in this regard. Frequency of vegetables intake was relatively higher than fruit intake among our participants. This inadequate intake was also noted in the Mongolian National Survey on the Prevalence of Non-Communicable Disease Risk Factors, revealing that Mongolians aged 15-64 consumed an average of 0.4 serving of fruits and 1.0 serving of vegetables per day. According to this survey, the majority of the population in Mongolia (96.4%) consumed less than 5 units of fruits and vegetables per day (Public Health Institute, Mongolia, 2013). In our study, smoking on an empty stomach was found to double the risk of gastric cancer, as similarly noted in other studies (Gantuya et al., 2018; Sambuu, 2012). Nevertheless, some studies have found that smoking increases the risk of gastric

cancer by approximately 1.53-fold depending on smoked years, the number of cigarettes smoked per day, and the presence of other risk factors, such as alcohol and drug abuse (Ladeiras-Lopes et al., 2008).

Having a family history of gastric cancer (first-degree) was also found to be a strong potential risk factor for gastric cancer in this study. Positive family history could be a risk factor as a result of a shared environment, for example, passing of *H. pylori* from parents to children, and/or because of shared genetic factors.

Moreover, a low PGI level and low PGI/II ratio were associated with gastric cancer risk in this study. Several studies have assessed the risk of gastric cancer by ABC(D) method (Park et al., 2016; Cho et al., 2017; Chen et al., 2018). Our study findings were consistent with those of other studies suggesting that group B to group D are more susceptible to gastric cancer . These studies have recommended patients in groups B, C, and D to undergo upper endoscopic examination at intervals of 3, 2, and 1 years, respectively. In Mongolia, gastric cancer morbidity and mortality are high, and more than 80 percent of new cases are diagnosed at late stage. Therefore, an annual upper endoscopy is recommended for individuals who are over 40 years of age. Given that the endoscopic and histological examination are invasive and uncomfortable for the patients, there is a demand to introduce a non-invasive, easy-to-use early detection method for screening of general population.

In conclusion, our findings suggested that gastric cancer risk was more closely associated with eating habits, smoking, family history, and precancerous lesions. ABC(D) method seems to be a plausible alternative or supplementary method for stratifying patients at high risk of gastric cancer in our country

Author Contribution Statement

None.

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Ethical approve

The study protocol was approved by Ethics Review Committee of Ministry of Health of Mongolia on 26 July, 2017 (approval number: 05).

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Conflict of interest

None of the authors have any conflict of interest.

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