The Clinicopathological Features and Staging at Presentation of Gastric Cancer: A Single-Center Retrospective Study

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Introduction  Gastric cancer (GC) is the third leading cause of cancer death, with most patients diagnosed at a later stage, with distant metastasis at the time of presentation, contributing to poor prognosis. GC has been associated with nonspecific clinical presentations, which cause a time delay for patients to seek for medical advice. This study aims to identify the clinicopathological features of GC patients and correlate time delay of the diagnosis to the staging of the disease.

Materials and Methods  This is a single-center retrospective study of GC patients diagnosed from January 2012 to December 2018. All relevant data of GC patient diagnosed during this time period were extracted from the patients' case notes.

Results  A total of 69 GC patients were included in this study, with male preponderance and mean age of 62 years old. The top three symptoms presented are dyspepsia or ingestion (47.8%), weight loss (43.5%), and nausea or vomiting (33.3%). The mean time delay was 3.7 months. Patients presented with weight loss have a significantly longer average time delay of 4.88 months. Most tumor lesion was found at the distal stomach (43.5%), while 74.5% tested negative for Helicobacter pylori. Most patients were diagnosed at Stage IV (52.6%) and Stage III (36.8%) of the disease, with poorly differentiated (67.7%) histological features which have poor prognosis.

Discussion and Conclusion  No evidence of specific symptom or combination of symptoms predicts higher risk of GC. Regardless of the number of symptoms presented or the time delay, most GC patients were diagnosed at later stage of the disease. The study shows the importance of GC screening in Malaysia to ensure early detection, even before a symptom presented.
alarming symptoms, may improve the prognosis of the disease. However, time delay in GC diagnosis remains a major issue in Malaysia. A study conducted among 112 gastric and esophageal cancer patients in Malaysia reported that the mean duration from the first appearance of cancer symptoms to endoscope procedure was 32.4 weeks, which is approximately 5 months. Although there is a study which suggested that diagnostic delay of 6 months for cases of uncomplicated dyspepsia may not have an effect on patient’s survival, but not enough evidence had been collected to show how other clinical presentations correlates to staging of the disease. It has been well-established that clinicopathological features of the tumors are important in evaluating the disease prognosis, likewise in deciding treatment regime.

This study therefore aims to identify common presentations of GC, features of the tumor, and cancer staging at the time of diagnosis in Penang Adventist Hospital. Meanwhile, time delay was also evaluated by identifying the duration from which the symptoms presented was first recognized by the patient to the time of diagnosis.

Materials and Methods
A retrospective review of patients diagnosed with GC at Penang Adventist Hospital, Malaysia, for the period January 2012 to December 2018 was performed. Relevant data has been extracted from patients’ case notes, including laboratory reports, oesophagogastroduodenoscopy (OGDS), and histological and imaging studies.

Definition and Stratification
Data of patient’s presenting symptoms are collected based on complaints recorded in the medical notes during the first visit. Imaging studies, such as OGDS and CT or PET-CT report, are based on the first report available during or after the first patient’s visit. Tumor sites are categorized into three parts, gastroesophageal junction, proximal and distal stomach, where proximal stomach includes the cardia, fundus and body, while distal stomach comprises the antrum and pylorus of the stomach.

Date of initial diagnosis of gastric cancer is based on the date of which the histological report was released. Information regarding the features of the tumor were extracted from the histological report in which the date of initial diagnosis was taken. Histological subtype of the gastric cancer was classified according to Lauren’s criteria as intestinal, diffused and indeterminate type. Tumor histological reports in which Lauren’s criteria were not mentioned were classified under indeterminate/unknown subtype.

Preoperative cancer markers, carbohydrate antigen (CA 19–9), and carcinoembryonic antigen (CEA) values were recorded, and each was classified into three groups. CA 19–9 value < 35 U/mL is classified as CA 19–9 Group 1, which is also recognized as negative. Patients with CA 19–9 between 35 and 100 U/mL were classified in Group 2, while those > 100 U/mL were classified in Group 3. Patients were recognized as negative for CEA marker when classified in CEA Group 1, with CEA value < 5 ng/mL. Patients with CEA value ranges between 5 and 30 ng/mL and > 30 ng/mL were classified in Group 2 and 3, respectively.

Statistical Analysis
The statistical analyses were done using SPSS software for Window version 23.0. A descriptive analysis for each parameter was performed, which included the mean, standard deviation (SD), frequencies and percentages for all demographic characteristics, presenting symptoms and staging of cancer at presentation. Missing data were excluded when statistical analyses were applied. The Mann–Whitney U test will be used to assess the difference of the means between two independent groups. Comparisons were done on qualitative data using Pearson’s Chi-squared test, where p < 0.05 was recognized as statistically significant.

Results
The study involved 69 patients (n = 69) diagnosed with GC from year 2012 to 2018 at Penang Adventist Hospital. The subjects included in the data analysis had a mean age of 62 years (SE = 1.679, median age = 62; range = 28–87) at the point of diagnosis. There were more male than female patients, with 42 males (60.9%) and 27 females (39.1%). Most patients were Chinese (60.9%), followed by Indonesians (36.2%), while Indians and other races constituted a minimal portion of this cohort, which is only 1.4% in each group. Mean body mass index (BMI) of the subjects is 23.15 (SE = 0.588). Patients with blood group O comprised the majority of the patients, 42.6%, followed by blood group A (29.8%), B (17.0%), and blood group AB being the least (10.5%).

Smokers and ex-smokers are categorized as one group. There were more non-smokers (65.2%) than smokers (34.8%) among the study cohort. Meanwhile, patients who reported to be alcohol drinkers only constituted 14.5%, while most (84.1%) did not drink alcohol. Patients with GC who were also afflicted with diabetes mellitus, hypertension and hypercholesterolemia were 14.5, 30.4, and 14.5%, respectively, of the total sample size.

Presenting Symptoms and Time delay for Diagnosis
Most patients presented to the clinic with complaint of dyspepsia or ingestion (47.8%), followed by weight loss and nausea or vomiting accounting for 43.5 and 33.3%, respectively. Other symptoms which are commonly reported included epigastric pain (24.6%), dysphagia (24.6%), anemia (15.9%), abdominal pain (14.5%), and bloating (13.0%). Symptoms which are only reported by five or less patients among the total subject group were categorized under “others,” including tiredness, altered bowel habit, altered taste, loss of appetite, chest pain/discomfort, melena, back pain, hematemeses, neck pain, flatulence, and syncope. As much as 31.9% of the patients exhibited at least one of the symptoms included in the “others” category.

Most patients complained of one to three symptoms during presentation. As much as 23.2% of the patients reported one symptom, 29% reported two symptoms, while 23.2% reported three symptoms. Only a small group of patient
Table 1  Demographic data distributed according to gender, ethnicity, blood type, smoking status, alcohol intake, and associated medical conditions (i.e., diabetes mellitus, hypertension and hypercholesterolemia)

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Percentage (%)</th>
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</thead>
<tbody>
<tr>
<td><strong>Gender (n = 69)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42</td>
<td>60.9</td>
</tr>
<tr>
<td>Female</td>
<td>27</td>
<td>39.1</td>
</tr>
<tr>
<td><strong>Ethnicity (n = 69)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>42</td>
<td>60.9</td>
</tr>
<tr>
<td>Indonesian</td>
<td>25</td>
<td>36.2</td>
</tr>
<tr>
<td>Indian</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Blood types (n = 47; missing = 22)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>14</td>
<td>29.8</td>
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<tr>
<td>B</td>
<td>8</td>
<td>17.0</td>
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<tr>
<td>O</td>
<td>20</td>
<td>42.6</td>
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<tr>
<td>No</td>
<td>5</td>
<td>10.6</td>
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<tr>
<td><strong>Smoking (n = 69)</strong></td>
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</tr>
<tr>
<td>Smoker/Ex-Smoker</td>
<td>24</td>
<td>34.8</td>
</tr>
<tr>
<td>Non-Smoker</td>
<td>45</td>
<td>65.2</td>
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<tr>
<td><strong>Alcohol (n = 69)</strong></td>
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</tr>
<tr>
<td>Drink alcohol</td>
<td>11</td>
<td>15.9</td>
</tr>
<tr>
<td>Do not drink alcohol</td>
<td>58</td>
<td>84.1</td>
</tr>
<tr>
<td><strong>Diabetes Mellitus (n = 69)</strong></td>
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<td></td>
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<tr>
<td>Yes</td>
<td>10</td>
<td>14.5</td>
</tr>
<tr>
<td>No</td>
<td>59</td>
<td>85.5</td>
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<tr>
<td><strong>Hypertension (n = 69)</strong></td>
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<td></td>
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<tr>
<td>Yes</td>
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<tr>
<td>No</td>
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<td>69.6</td>
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<td><strong>Hypercholesterolemia (n = 69)</strong></td>
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<tr>
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<td>10</td>
<td>14.5</td>
</tr>
<tr>
<td>No</td>
<td>59</td>
<td>85.5</td>
</tr>
</tbody>
</table>

Table 2 shows that the patient group which showed weight loss had a significantly longer mean time delay compared with the group of patients who did not experience weight loss ($p \leq 0.05$). Interestingly, loss of weight is also the presenting symptom which has the longest time delay, with a mean time delay of 4.88 months in the positive group, and an average difference of 0.88 month time delay compared with the other symptoms.

Clinical Findings and Tumor Features

OGDS reports ($n = 61$) shows that tumor is observed during the OGDS procedure in 68.9% of the cases. As much as 50.8% have ulcer present, while gastritis and esophageal reflux were present in 27.9 and 21.3% of the cases, respectively. Most tumor or lesion are found at the distal part of the stomach (43.5%) followed by proximal stomach (37.1%) and gastroesophageal junction (19.4%) with $n = 62$. Crosstab analysis shows that 64.7% of those with dysphagia had tumor at the gastroesophageal junction, with $p < 0.05$ indicating association of dysphagia with tumor at the gastroesophageal junction. However, this has an expected count of less than five, which may indicate inaccuracy of this statistics. Chi-squared test shows no significant associations between the site of tumor and other presenting symptoms. Among 61 subjects whose OGDS reports were available, only 25.5% of the biopsies done tested positive for *Helicobacter pylori* (Table 3).

Histological studies show that all of the cases recorded showed adenocarcinoma. As much as 67.7% are poorly differentiated, 27.4% are categorized as intermediate, while only 4.8% are well-differentiated. In 41.8% of the cases, Signet ring cell was present. The type of gastric tumor was classified based on Lauren’s criteria, where 26.5% were part of the intestinal group, 35.3% were diffused, and the majority (38.2%) were indeterminate/unknown (Table 4). Tumor marker CA 19.9 and CEA markers were lower in most GC patients among the study subjects at the time of diagnosis. CA 19.9 < 35 U/mL, referring to the negative group, accounts for 60% of the cases ($n = 50$). Only one of the GC cases has 35–100 U/mL (2%), while 38% has elevated CA 19.9 level. CEA marker was available in 54 of the reports ($n = 54$), with 72.2% of the patients having a very low value, <5 ng/mL. As much as 18.5% had CEA marker reading ranging from 5 to 30 ng/mL and only 9.3% had > 30 ng/mL. CEA markers at baseline (Table 5).

Staging at Presentation

Most patients with GC were diagnosed to be at the later stage at the time of presentation. Among 57 patients whose stage of cancer was appropriately assessed or documented, 30 were diagnosed with Stage IV (52.6%), 21 out of 57 (36.8%) were in Stage III, 8.8% diagnosed with Stage II, while only one patient out of 57 (1.8%) was in Stage I at the time of presentation. Crosstabs analysis on the relationship between each presenting symptom and stage of the disease at presentation shows no evidence of an association using standard Chi-squared test of independence. Duration of time delay in diagnosis also shows insignificant difference between stages of GC. There is no significant difference of CA 19.9 and CEA cancer marker...
Discussion

The results of this study show a male preponderance (60.9%) in GC patients, with mean age of 62 years. This supports global epidemiological studies, where GC was diagnosed in males 2.2 times more compare with females, which may due to protective effect of estrogen against GC.6 This idea was further enhanced by the presence of estrogen receptor-β in GC tumor that may protect against invasiveness in GC.5 Most patients were Chinese and Indonesian, who are the primary service users at the Penang Adventist Hospital. There were a larger proportion of patients who had blood group O (42.6%) compares with blood group A (29.8%). This contradicts with most studies which suggest that blood group A will have higher risk of GC than blood group O. A study suggested that although GC is more commonly associated with patients with blood group A, GC in blood group O is associated with increased risk of peptic ulcer disease, which could eventually increase the risk of GC.8 Therefore, this finding suggests that the development of GC among most patient in this study cohort may be associated with peptic ulcer disease or other risk factors.

Furthermore, there were only small number of patients (25.5%) who tested positive for *H. pylori* infection in this study, which was known to be one of the main risk factors for GC and peptic ulcer disease.6 These data suggested other etiologies that may have contributed to the development of GC among the Penang population. Although both smoking and alcohol drinking are known risk factors for GC,8 the results found in this study shows unexpected demographics, with a
higher proportion of nonsmokers (65.2%) and nonalcoholics (84.1%). This may be due to self-report bias among the study cohort, where subjects would tend to deny smoking and alcohol consumption when presented in the clinic, or referred themselves as nonsmokers or nonalcoholics due to the recent intake,\textsuperscript{10,11} and lack of vegetables and fruits\textsuperscript{12} among the general population in Indonesia and Malaysia could be the main contributing factor of GC development in this study cohort. However, since this was not the main focus of the research, and most GC studies conducted in Malaysia often excluded Penang due to its unique population,\textsuperscript{2} further studies involving a larger sample size, focusing on understanding GC etiology among the Penang population, is needed to support this finding.

The top three complaints presented among the study cohort were dyspepsia/ingestion (47.8%), weight loss (43.5%), and nausea/vomiting (33.3%), with mean time delay of 3.7 months. All the symptoms presented are nonspecific, suggesting the importance of implementation of GC screening; also, general practitioners should have a greater level of suspicion among high-risk patients to diagnose GC. While endoscopic procedure delay may not be applicable in private healthcare settings in Malaysia, the tendency of the general population in Indonesia and Malaysia could be the main contributing factor of GC development in this study cohort. Moreover, most patients present with only one to three symptoms, suggesting the importance of implementation of GC screening; also, general practitioners should have a greater level of suspicion among high-risk patients to diagnose GC. Primary care should take note of patient’s symptoms and suspect GC in high-risk patient group, even though patient does not exhibit alarming symptoms. This is evident in countries such as Japan and Korea, where a decrease of incidence and mortality of GC was observed through the implementation of GC screening.\textsuperscript{14,15}

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Howbeit, the cost-effectiveness of
implementing such screening in other countries with relatively lower incidence rate remains debatable and the subsequent issue of overdiagnosis through screening program should be carefully addressed. Although there is no significant difference between the stages of cancer at presentation among patient groups that were diagnosed within the time delay of 3 months, between 3–6 months and 6 months, our study has shown that further delay of approximately one month (0.88 month) will lead to presentation of weight loss, which may be an indication of disease progression. Weight loss was known to be associated with poor prognosis, where a study has shown the significance of preoperative weight loss as an independent prognostic factor for GC, especially when weight loss is above 10%. In this study, most GC was found at the distal stomach (43.5%) and patients were mostly diagnosed at the later stage with poorly differentiated (67.7%) histological structure of the tumor. A study conducted in Malaysia showed that the Chinese population are more likely to have gastric adenocarcinoma located at the noncardia or distal region (73.7%), while all Chinese possessed diffuse subtype. This explains the common tumor features seen in this study, since the study cohort is largely made up of those with Chinese ethnicity and Indonesians, who may also be of Chinese origin. Regardless of the time delay and the number of presenting symptoms the patients reported, most patients were diagnosed at an advanced stage, where 52.6% were in Stage IV and 36.8% were in Stage III upon diagnosis. As much as 67.7% had poorly differentiated tumor, which has a poor prognosis. Meanwhile, most GC patients in this study cohort were part of the negative group for CA19.9 and CEA tumor markers, where 60% had < 35 U/mL CA19.9 reading and 72.2% has CEA tumor marker < 5 ng/mL. This could mean that CA 19.9 and CEA tumor marker studies are not suitable to be used as screening tool in GC; however other studies have shown prognostic values, especially CEA marker in early GC, although the usefulness of both tumor markers remain debatable.

**Limitation of the Study**

Since the study adapted a retrospective analysis design, statistical biases due to missing data, which were not collected or documented at the point of time, were inevitable. Selection bias emerged mostly because the study was conducted in a single center, in which the study cohort comprised mainly Chinese and Indonesians, due to the uniqueness of Penang as a medical tourism spot. As discussed above, further studies are required to conclude the significance of other etiologies in GC development in Penang, correlation of clinicopathological features of GC, and stage of the disease at presentation.

**Conclusion**

Dyspepsia, loss of weight, and nausea/vomiting were the top three symptoms presented among the study cohort. There is no evidence of specific symptom or combination of symptoms which would indicate higher risk of GC. Regardless of the number of symptoms presented by the patients and the time delay for diagnosis, most GC patients are diagnosed at the later stage of the disease, which has poor prognosis. This study therefore demonstrates the importance of development of GC screening criteria for high-risk patients based on risk factors and demographics, even prior to any symptoms presented. This is because there have been no significant presenting symptoms that could indicate an early stage of GC, neither is there a cutoff time which could be used as guideline for the general public on when to visit a clinic when a presenting symptom persisted for a period of time (i.e., time delay). Healthcare professionals may lower the threshold to perform OGDS, especially on elderly patients who have gastrointestinal-related symptoms over a span of time to ensure early detection. Further studies are required to provide guidelines for primary care practitioners on referring patients to OGDS. More importantly, there is a need to increase awareness of gastric cancer to decrease the time delay for patient to visit the clinic or being referred to a gastroenterologist.

**Note**

The study was approved by the Penang Adventist Hospital Ethics Research Committee (Action No.: RC2019–002) and the Perdana University Institutional Review Board (Ref No.: PU-IRB/MKV/0214/510). None declared.

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