

MARK's Quadrant scoring system: a symptom-based targeted screening tool for gastric cancer

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Abstract

Background Gastric cancer is notably one of the leading causes of cancer-related death in the world. In Malaysia, these patients present in the advanced stage, thus narrowing the treatment options and making the surgery nearly impossible for successful curative resection. Failure to identify high-risk patients and delay in diagnostic endoscope procedure contributed to the delay in diagnosis. The aim of the study was to develop and validate a scoring system (MARK's Quadrant) which can identify symptomatic patients who are at risk for gastric cancer.

Methods A 3-phase approach was undertaken: Phase 1: development of the weighted scoring system; Phase 2: estimating positive predicting value of MARK's Quadrant; and Phase 3: a) testing the validity of MARK's Quadrant in an open-access endoscope system; and b) comparing its usefulness compared to conventional referral system.

Results In phases 1 and 2, MARK's Quadrant with weighted symptoms was developed. The sensitivity of MARK's Quadrant is 88% and the specificity is 45.5% to detect cancerous and precancerous lesions of gastric. This was confirmed by the prospective data from phase 3 of this study where the diagnostic yield of MARK's Quadrant to detect any pathological lesion was 95.2%. This score has a high accuracy efficiency of 75%, hence comparing to routine referral system it has an odds ratio (95%CI) of 10.98 (4.63-26.00), 6.71 (4.46-10.09) and 0.95 (0.06-0.15) (P<0.001 respectively) for cancer, precancerous lesion and benign lesion diagnosis respectively.

Conclusion MARK's Quadrant is a useful tool to detect early gastric cancer among symptomatic patients in a low incidence region.

Keywords Open-access endoscope, targeted screening, early gastric cancer

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Introduction

Gastric cancer is the second most common cause of cancer-related death in the world [1]. Detecting this cancer early has been an uphill task for decades. Most of the patients with gastric cancer present with advanced diseases. Overall

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survival of gastric cancer patients has not improved in the last two decades.

In 1962, the Japanese Society of Gastroenterological Endoscopy introduced the definition of early gastric cancer (EGC) as a malignant tumour limited to the mucosa or submucosa irrespective of the presence of lymph node metastases [2]. Many Japanese series have consistently reported 5- and 10-year survival rates of over 90% for EGC [3-7]. In Japan, up to 60% of gastric cancers are diagnosed as EGC [8]. This may be due to a mass screening program initiated in the 1960s for those above the age of 40 years.

In Western countries however, EGC is less frequently detected, only accounting for 10-20% of all gastric cancers [9]. Mass screening programs are not cost-effective in a region where the incidence rate of gastric cancer is moderate or low. Hence, targeted screening focused on populations at high risk for these cancers.

Screening of symptomatic patients through open-access endoscope (OAE) has been reported to increase the incidence of EGC in many countries. In Birmingham, a program to screen dyspeptic patients over the age of 40 years in the 1990s

resulted in an improvement in EGC detection from 1 to 26%. As a result, curative resections were increased from 20 to 63% during the same period [10]. Similar result has been reported in Leeds, where the incidence of EGC increased from 4% in 1970 to 26% in 1980 [9] using similar programs.

In Malaysia gastric cancer is one of the ten most common cancers. The majority of gastric cancer patients are diagnosed with advanced disease. Most often treatment modalities are narrowed towards palliative procedures rather than curative resections [11,12]. Poor outcome of gastric cancer patients in Singapore was reported due to late presentation of these patients to the hospital [13].

The aim of this study was to develop and validate a symptom-based targeted screening tool to identify patients at risk for gastric cancer. This tool should aid primary care physicians to identify high risk patients for gastric cancers.

Materials and methods

Study design

In general, development of diagnostic criteria involves assessment of probability laws and concepts. Ultimately, this information will predict the presence or absence of a particular disease from the status of presenting symptoms (i.e. present or absent). In any screening test, there may be the eventuality of yielding a false positive (i.e. chances for the test to show a positive status even when the true status is negative) or a false negative (i.e. when a test indicates a negative status even when the true status is positive) [14].

This is a derivative and validation study (diagnostic validation) of symptom score to diagnose gastric cancer in a low-incidence region. This study is divided into three phases (Fig. 1).

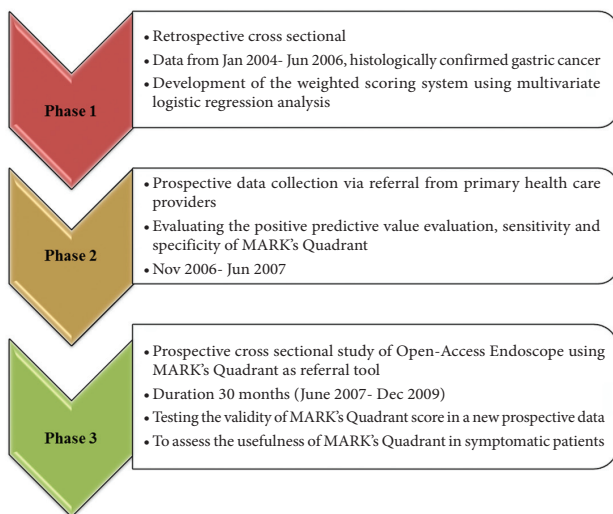


Figure 1 Summary of three phase methodology

Phase 1: Development of the weighted scoring system

A non-weighted symptom, gender and race referral criteria was grouped/listed based on retrospective data from Jan 2004-2006 of all histological confirmed gastric cancer patients diagnosed at our center. Using this data we developed a weighted symptom list for our local population.

By modeling the relationship between the list of criteria and diagnosis, a weight was determined for each criteria/symptoms in the list. For each criterion, the weights were derived based on the multivariate logistic regression model, via statistic software designed to take in all the list of criteria and predict the probability of the presence of stomach cancer and its precancerous lesions. A score (weight) was assigned according to the odds ratio of each criterion with ratio of 1:1 (Table 1).

In order to provide a model representative of a wider community, a cross validation technique was used in which several logistic regression criteria were produced and their respective coefficients were averaged. The average values were rounded to the nearest whole number to give the criteria weights prior to summing to produce the weighted scores.

The model associates each question on the criteria list with a coefficient reflecting the relative importance of that symptom/criteria in determining the probability of presence of gastric cancer and its precancerous lesions. A positive value coefficient influences towards a decision that the individual is classified as a cancer patient or having a precancerous lesion of the stomach. A negative value coefficient influences away from a decision that the patient has stomach cancer and its precancerous lesions.

Phase 2: Estimating positive predicting value of MARK's Quadrant (MQ)

A scoring system was developed using prospective data in order to estimate its positive predictive value (PPV). These weighted criteria were grouped into age, modified ALARM symptoms, dyspepsia and history of upper GI bleed to create a new scoring system called MQ.

A prospective patient collection from November 2006 to June 2007 was used to assess the diagnostic accuracy by estimating PPV of MQ (Table 2) in detecting stomach cancer and its precancerous lesion in the community using patients referred via OAE service.

Patients who fulfil any criteria in MQ at the primary care centres in the state of Negeri Sembilan are referred to Tuanku Ja'afar hospital Seremban via OAE. In this new referral system (OAE), patients who fulfil any criteria in MQ will have a gastroduodenoscopy procedure done within 2 weeks without prior assessment in the specialist clinic. All the endoscopy procedures are done according to the European Society of Gastrointestinal Endoscopy (ESGE) recommendations for quality of endoscopy. In patients where no suspicious lesions are seen, two biopsies are taken from antrum and body of the stomach.

Table 1 The MARK's list with associated weighted criteria

No	Criteria	Odds ratio (95%CI)	Criterion weights
1	*Age [<40 yrs]	2.27 (1.11-3.62)	2
2	*Age [40-49 yrs]	3.62 (1.77-4.52)	3
3	*Age [>50 yrs]	5.32 (3.22-8.12)	5
4	**Malay	1.51 (1.34-3.81)	2
5	**Chinese	1.67 (1.53-3.61)	2
6	**Indian	1.57 (1.12-3.21)	2
7	+Sex - Male	1.32 (1.12-2.31)	1
8	+Sex - Female	1.13 (1.01-2.55)	1
9	Melena more than 1 yr	1.05 (1.01-2.11)	1
10	Melena less than 1 yr	5.45 (2.31-7.62)	5
11	Anemia	3.32 (2.15-3.71)	3
12	Epigastric mass/fullness	3.41 (2.35-4.78)	3
13	Persistent vomiting	3.47 (2.55-4.21)	3
14	Significant loss of weight	3.11 (2.67-5.72)	3
15	Dysphagia	4.87 (2.66-8.19)	5
16	Early satiety/eating less over a period of time	2.77 (1.02-3.71)	3
17	Dyspepsia, intermittent more than 1 yr	2.18 (1.53-3.21)	2
18	Dyspepsia, intermittent less than 1 yr	3.22 (1.71-4.11)	3
19	Dyspepsia, persistent for >2 weeks	5.44 (2.67- 8.32)	5

*Age was divided into 8 categories. The bottom three and the top three age groups were combined according to the national cancer registry 2002

**Race was excluded from the final MARK's quadrant due to similar score and combined marriage among the population

+Gender was excluded in view of no significant difference in the odds ratio

The estimate of PPV for the various score thresholds depends on the fact that higher score correspond to higher probability of having gastric cancer or its precancerous lesions. The weighted scoring system is valid if it can be shown to retain this property when applied to a new set of data.

Phase 3: a) Testing the validity of MQ score in a new data set and b) Comparing MQ usefulness compared to conventional referral system

In this phase, to validate the positive predictive value of MQ, it was tested in a new set of prospective data from a new patient referred via OAE. This new data was compared with the conventional endoscope referral system. The conventional endoscope referral system in our centre involves the patients who are referred; seen by specialist in the clinic before being given an appointment for endoscopic procedure. Hence, in the new OAE system, high-risk patients (with MQ score of 10 and more) will come directly for endoscopic procedure only. This filtering system using MQ helps identify the high-risk patients, thus diagnostic endoscopies are done earlier. The endpoints compared included time duration taken from referral to endoscopy, early cancer detection, detection of precancerous lesion, negative endoscopy, and total diagnostic yield.

Precancerous condition/lesions of the stomach in this study included any of the following: dysplasia of any grade in the stomach; intestinal metaplasia of the stomach of any grade; *Helicobacter pylori* (*H. pylori*) infection with or without chronic active gastritis; and atrophic gastritis. All the above conditions are defined according to the Sydney system of classification and grading of gastritis 1994 [15]. Cancerous lesions are defined as any malignant lesions/mass of stomach of any type and grade. All diagnoses are confirmed by histopathological examination.

Sample population

In phase 3, only patients who fulfil the criteria in MQ score of 10 or more (Table 2) were included in the study. All patients with the above criteria presented to district clinics, primary health care centers and district hospitals were counseled and given endoscope appointment via phone. We excluded the following patients from the analysis: patients who underwent an esophagoduodenoscopy in the last 12 months and/or were under follow-up; patients who were already diagnosed with gastric or esophageal cancers; patients who underwent asurgery for GI malignancy; acute GI bleeding (emergency cases); and patients who were admitted for complications owing to upper GI malignancies.

Table 2 The MARK's Quadrant - targeted screening tool for gastric cancers

Quadrant A: Dyspepsia		Quadrant B: Recent UGIB (including melena)	
	Score		Score
Intermittent, more than 1 yr	1	Occurred more than 1 yr ago	1
Intermittent, less than 1 yr	3	Occurred less than 1 yr	5
Persistent for 2 wks	5		
Quadrant C: Modified alarm symptoms		Quadrant D: Age	
	Score		Score
Anemia	3	Less than 40 yrs	2
Epigastric Mass / Fullness	3	40 – 49 yrs	3
Persistent vomiting [>2 wks]	3	≥ 50 yrs	5
Significant loss of weight	3		
Dysphagia	5		
Early satiety / eating less over a period of time	3	Total score:	

A score of 10 and above will be deemed as high risk for gastric cancer and warrant an urgent upper endoscopy
 *UGIB, upper gastrointestinal bleeding

Statistical analysis

The statistical analyses for the first and second phase were part of internal validation process using retrospective data as stated above. In these phases, multivariate logistic regression test and appropriate chi square were used. A contingency table analysis (or two-way table) was done to identify the probability estimates on the cancer and precancerous conditions and the screening test results. In the third phase, external validation using prospective data and comparison of diagnostic yield from two different referral systems were done using Pearson's chi square analysis. All data were analyzed using SPSS ver 17.

Ethical approval

This study was approved by the Research Ethical Committee of Tuanku Ja'afar Hospital in September 2006. All patients recruited gave informed consent for the endoscopy procedures.

Results

Phase 1

A total of 250 stomach cancer patients' data were reviewed to gather this list of criteria. The most influential criteria toward the diagnosis of stomach cancer and its precancerous lesion of the stomach were: persistent dyspepsia ≥ 2 weeks (OR 5.44; 95%CI 2.67-8.32); age >50 years (OR 5.32; 95%CI 3.22-8.12); and recent history of upper GI bleed (OR 5.45; 95%CI 2.31-7.62) (Table 1).

In this analysis, the gender and race were seen to have similar weight. Hence, when used in combination with other criteria,

these criteria did not contribute as screening tools to detect the presence of stomach cancer and its precancerous lesion.

Phase 2

In this prospective phase; a total of 180 patients were analyzed. The mean age of these patients was 58 years (SD 17.12). The majority of them were male (65.8%). Ethnic distribution between Malay, Chinese and Indian were 40%, 32.5% and 27.5% respectively.

Lowering the threshold MQ (Table 2) score below 10 progressively decreased the expected efficiency of detecting cancer and its precancerous lesion below 80% diagnostic yield for stomach cancer and precancerous lesion. Thus performing endoscopic procedures for patients scoring MQ less than 10 would only increase normal findings and benign lesion and would reduce the sensitivity and positive predictive value (Table 3).

Of the 180 patients in this sample group, 77.8% (140 patients) scored above 10 and 22.2% (40 patients) scored below 10. Of these, 110 (78.6%) patients exhibited pre-cancerous and cancerous conditions of the stomach and 21.4% (n=30) were negative for these conditions. In contrast, of the 40 patients who scored below 10, only 37.5% (n=15) exhibited pre-cancerous and cancerous conditions of stomach and 62.5% (n=25) were negative for these conditions.

Based on the conditional probability estimation, the probability of a patient exhibiting pre-cancerous and cancerous conditions, given that he/she has a score of above 10, is 88% (sensitivity). Similarly, the probability of MQ scoring below 10 (absence of symptoms) given the absence of the cancerous and precancerous condition of stomach is 45.5% (specificity). In this group, 78.6% of these patients had cancerous or/and precancerous lesions. Positive predictive value was 79.3% and negative predictive value was 62.5% with an accuracy of 75% for diagnosis of gastric cancer and precancerous lesion (Table 4).

Table 3 Positive predictive value estimated for the weighted scoring (MARK's Quadrant score) applied to all patients referred via open-access endoscopy service from November 2006 to June 2007

Total score	Number of patients above threshold	Cancer	Precancerous lesions	Benign	Normal	Positive predictive value of stomach cancer	Positive predictive value of stomach cancer precancerous lesion
>25	15	3	10	2	0	20.00	86.67
20	25	4	20	1	0	16.00	96.00
19	37	5	31	1	0	13.51	97.30
18	44	5	38	1	0	11.36	97.73
17	56	5	47	4	0	8.93	92.86
16	66	7	54	4	1	10.61	92.42
15	75	7	61	6	1	9.33	90.67
14	98	8	74	14	2	8.16	83.67
13	110	10	80	15	5	9.09	81.82
12	112	12	80	15	5	10.71	82.14
11	125	15	88	16	6	12.00	82.40
10*	138	18	88	21	11	13.04	76.81
9	140	19	88	22	11	13.57	76.43
8	148	19	91	24	14	12.84	74.32
7	156	19	96	25	16	12.18	73.72
6	165	19	100	25	21	11.52	72.12
5	172	19	104	28	21	11.05	71.51
4	180	19	112	28	21	10.56	72.78
3	180	19	112	28	21	10.56	72.78
All	180	19	112	28	21	10.56	72.78

*The score of 10 is designated as the cut-off for high risk patients with predictive value of more than 80%

Phase 3: Testing the validity of MQ score in a new data set

The third phase confirmed that higher scores correspond to higher probability of having stomach cancer or its precancerous lesion in the independent test subset of OAE data from Jul 2007 to Dec 2009. Total of 210 patients were included in this phase via OAE using MQ score above 10.

In general, the average age of these patients was 55 years. The majority of them were male (62.4%) and Malay (44.3) (Table 5). A total of 18 stomach cancers were diagnosed using

MQ as a screening tool. Two of these cancers were early stomach cancers in stage Ib & IIa.

From the 210 patients who underwent targeted screening under the OAE, 18 (8.6%) patients were found to have stomach cancer and 144 (68.6%) were found to have one of the precancerous lesions of the stomach such as intestinal metaplasia, dysplasia, *H. pylori* infection with chronic active gastritis and atrophic gastritis. Benign lesion and normal scope findings were found in 38 (18.1%) and 10 (4.8%) of the patients in this group respectively (Fig. 2).

Table 4 Bayes analysis of patients with MARK's Quadrant scores >10 and <10

MARK's score	Cancer and Pre-cancerous conditions present (<i>positive</i>)	Cancer and Pre-cancerous conditions absent (<i>negative</i>)	Total
Scores >10	110 (78.6)	30 (21.4)	140 (100)
Scores <10	15 (37.5)	25 (62.5)	40 (100)
Total	125	55	180

The brackets represent percentages; $\chi^2 = 11.76$, degrees of freedom = 1, $P = 0.0006$

Sensitivity = 88%; Specificity = 45.5%; Positive predictive value = 79.3%;

Negative predictive value = 62.5%; Accuracy = 75% for diagnosis of gastric cancer and precancerous lesions

Table 5 Demographic analysis of 210 patients from open-access endoscopy (OAE) and conventional system in the prospective data collection from July 2007 to November 2009

		Routine referral system	OAE (MARK's Quadrant >10)
Age [yrs] SD		52 [12.5]	55 [15.12]
Gender n[%]	Male	521 [52.1]	131 [62.4]
	Female	477 [47.8]	79 [37.6]
Ethnic group n[%]	Malay	438 [43.9]	93 [44.3]
	Chinese	319 [32]	59 [28.1]
	Indian	241 [24.2]	58 [26.6]

b) Comparison of usefulness of MQ compared to conventional referral system

The same data were used to compare and evaluate the OAE using MQ score as referring criteria to the conventional referral system (control). In the conventional system of referral of symptomatic patients during the same period (Jun 2007-Nov 2009), there were 998 patients referred via the conventional system (control). This group was compared to the OAE group which had 210 patients during this period. All patients who were referred via OAE were scoped within 2 weeks prior to surgical clinic appointment (Fig. 3).

Stomach cancers were diagnosed in 10 (1%) patients in the routine referral system and 18 (8.6%) patients in the OAE group. No EGCs were diagnosed in the routine referral system. Precancerous lesions were found in 144 (68.6%) patients in the routine referral system and 236 (23.6%) patients in the

OAE group. Benign lesions were found in 38 (18.1%) patients in the routine referral system and 415 (41.6%) patients in the OAE group. Normal findings were found in 337 (33.8%) patients in the routine referral system and 10 (4.8%) patients in the OAE group (Table 6).

Further analysis shows a significant difference between the OAE and routine referral system in terms of cancer diagnosis, precancerous lesion and benign lesion with odds ratio value of 10.98, 6.71 and 0.095 (P-value <0.001) respectively.

Hence, this preliminary study indicates that patients who score above 10 have a significantly higher likelihood of exhibiting pre-cancerous and cancerous conditions than patients who score below 10 (Table 6). The diagnostic yield of the routine referral system was 66.2% and the MQ group was 95.2% in diagnosing any pathological lesions in the stomach (P<0.001). Distribution of diagnosis among patients in both referral systems was different. In routine system, there were significantly more normal findings (33.8%) and benign lesions (41.6%) than stomach cancer (1%) and precancerous lesions (23.6%) of the stomach. On the other hand, MQ group found more precancerous lesions (68.6%) and stomach cancers (8.6%) compared to the routine referral system (Table 6).

Discussion

Targeted screening is useful to detect gastric cancer in low incidence regions such as Malaysia. We developed new criteria to identify high-risk patients in our local setting using a new symptoms based scoring tool (MQ) to detect gastric cancers early.

Most of the criteria used in previous studies either use the symptoms [16-18] or biochemical markers [18,19] such as serum pepsinogen and *H. pylori* antigen to identify high-risk patients. Nevertheless, all these criteria have their merits and limitations but these markers have given us a better chance to diagnose, detect and treat gastric cancers early. In low incidence regions, testing *H. pylori* antigen and serum pepsinogen for all patients may be costly in primary healthcare centers [20].

The OAE service is a fast tract method to reduce the delay in diagnosis of gastric cancer. Before the introduction of this service in our center, many primary care physicians empirically treated these patients with antacids or proton pump inhibitors. This only delays the diagnosis and treatment of the gastric cancer patients [21].

Tuanku Ja'afar Hospital Seremban (HTJS) is the first hospital in Malaysia to have a targeted screening program to detect high-risk patients for gastric cancer. MQ has been successfully used as the screening tool to detect gastric cancers.

Our experience with OAE services in 28 months resulted in 210 referrals with MQ score of 10 and above. All these endoscopies were done within 2 weeks of referral. This automated process of referral using MQ as a tool has eliminated delay in endoscopy for high-risk patients; since the endoscopic procedure can be ordered without prior specialist clinical assessment.

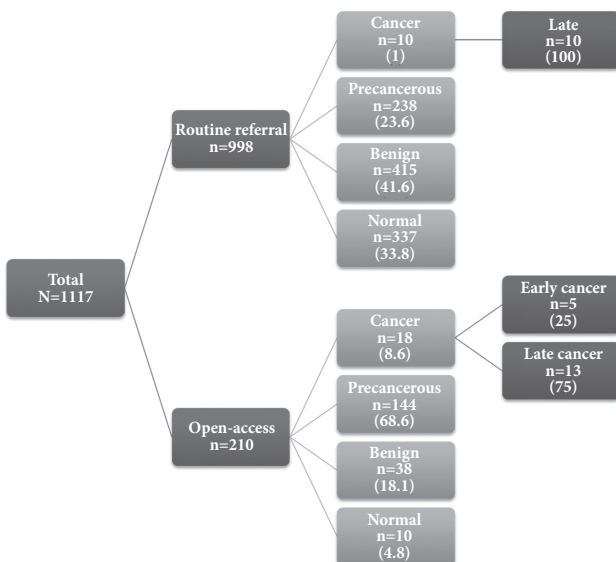


Figure 2 The diagnostic comparisons between routine referral system and open-access referral system using MARK's Quadrant as screening tool

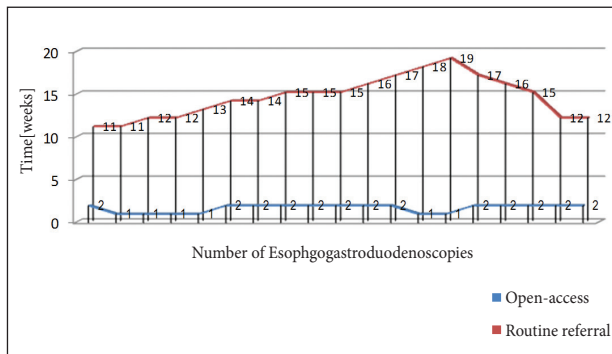


Figure 3 Average time taken from primary care physicians referral to endoscope procedure between routine system and open-access endoscopy (using MQ)

Before introduction of OAE services in HTJS, more than 90% of gastric cancer patients presented at advanced stages. Targeted screening indeed increased the awareness of primary care physicians and patients themselves to come early to hospital-if they have any of the high-risk symptoms or fulfil the MQ score. The diagnostic yield of targeted screening using MQ was calculated to be 95.2% as compared to the routine referral system which was 66.2%.

In a review of OAE in South Tees, Suvakovic *et al* have identified a number of the reasons for delay in diagnosis such as pre-treatment before endoscopy and failure to identify high-risk patients early. He highlighted there is a need for endoscopy guidelines to increase the diagnostic yield of early cancer [22].

The success of the OAE service in our study was due to frequent reminders in the form of continuous medical educational (CME) lectures, feedback of endoscopic findings to the primary care physician and a strict guideline for endoscopy to sustain awareness and standardize quality of service.

Our results suggest that sending patients with MQ score

of 10 and above for diagnostic testing (i.e. endoscopy) would be able to identify early cancer or precancerous conditions of stomach in a symptomatic patient and this allows for early effective treatment for these patients. We diagnosed two EGCs in this study. This indicates that appearance and severity of symptoms can also occur in early cancers.

Targeted screening should become an integral part of a public health policy, whereby early diagnosis/detection is the key to improved survival of gastric cancer patients. Patients with dyspeptic symptoms should be investigated early instead waiting for classical symptoms of gastric cancer [11,12]. There is an urgent need for clinicians to change their approach to the management of dyspepsia which is the commonest symptom of gastric cancer.

In this study, we have diagnosed 25 gastric cancers with two early cancers and a large number of pre-cancerous lesions. Diagnosing pre-cancerous lesions may give us the opportunity to treat, monitor and set surveillance strategies for these lesions. *H. pylori* infection and other gastric lesions can be treated to reduce the risk of developing cancer subsequently.

Diagnosing early cancers has its advantages; firstly diagnosing EGC gives a greater survival benefit to the patients [3]. Secondly, the cost of treating EGC is much lower when compared to treating late gastric cancer which may include systemic chemotherapy and palliative procedures.

The sensitivity of MQ is about 88% and specificity is 45.5%. This is remarkable for a scoring system such as MQ which only uses symptoms and not chemical indices for detecting cancerous and precancerous lesions of stomach. High diagnostic yield of MQ means unnecessary endoscopy can be avoided and more attention can be given to the high-risk patients.

In conclusion, MQ is a useful tool to identify high-risk patients for gastric cancer in moderate and low incidence regions. Subsequently, this scoring system would enable us to diagnose gastric cancers early in symptomatic patients.

Table 6 Comparison and odds ratio (OR) of diagnostic value of MARK's Quadrant as diagnostic tool between two referral systems

Diagnosis	Routine referral group N [%]	Open-access group [using MQ] N [%]	P value	95% Confidence interval/ odds ratio
Total	998 (100)	210 (100)		
Cancer	10 (1)	18 (8.6)	<0.0001	4.63-26.00 OR 10.98
Pre-cancerous	236 (23.6)	144 (68.6)	<0.0001	4.46-10.09 OR 6.71
Benign	415 (41.6)	38 (18.1)	<0.0001	0.061-0.149 OR 0.095
Normal	337 (33.8)	10 (4.8)		
Endoscopic diagnostic yield of positive findings (%)	66.2	95.2	<0.0001	

Summary Box

What is already known:

- The screening of symptomatic patients through open-access endoscopy has been reported to achieve a higher incidence of early gastric cancer (EGC)
- It has been reported that 60-90% of patients with EGC have dyspeptic symptom, but this symptom is discernible from other benign gastric diseases

What the new findings are:

- MARK's Quadrant (MQ) is a symptom-based targeted screening tool aimed to stratify high-risk patients for gastric cancer
- This tool is able to identify high-risk patients and reduce delay in diagnosis of gastric cancer MQ has a high diagnostic yield of precancerous and cancerous lesions
- MQ has been used successfully as a referral tool for high-risk endoscopy by primary care physicians in low incidence regions of gastric cancer

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