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Original research

Severity of gastric intestinal metaplasia predicts the risk of gastric cancer: a prospective multicentre cohort study (GCEP)

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ABSTRACT

Objective To investigate the incidence of gastric cancer (GC) attributed to gastric intestinal metaplasia (IM), and validate the Operative Link on Gastric Intestinal Metaplasia (OLGIM) for targeted endoscopic surveillance in regions with low-intermediate incidence of GC.

Methods A prospective, longitudinal and multicentre study was carried out in Singapore. The study participants comprised 2980 patients undergoing screening gastroscopy with standardised gastric mucosal sampling, from January 2004 and December 2010, with scheduled surveillance endoscopies at year 3 and 5. Participants were also matched against the National Registry of Diseases Office for missed diagnoses of early gastric neoplasia (EGN).

Results There were 21 participants diagnosed with EGN. IM was a significant risk factor for EGN (adjusted-HR 5.36; 95% CI 1.51 to 19.0; p<0.01). The age-adjusted EGN incidence rates for patients with and without IM were 133.9 and 12.5 per 100 000 person-years. Participants with OLGIM stages III–IV were at greatest risk (adjusted-HR 20.7; 95% CI 5.04 to 85.6; p<0.01). More than half of the EGNs (n=4/7) attributed to baseline OLGIM III–IV developed within 2 years (range: 12.7–44.8 months). Serum trefoil factor 3 distinguishes (Area Under the Receiver Operating Characteristics 0.749) patients with OLGIM III–IV if they are negative for *H. pylori*. Participants with OLGIM II were also at significant risk of EGN (adjusted-HR 7.34; 95% CI 1.60 to 33.7; p=0.02). A significant smoking history further increases the risk of EGN among patients with OLGIM stages II–IV.

Conclusions We suggest a risk-stratified approach and recommend that high-risk patients (OLGIM III–IV) have endoscopic surveillance in 2 years, intermediate-risk patients (OLGIM II) in 5 years.

Significance of this study

What is already known on this subject?

- Gastric intestinal metaplasia (IM) is a commonly diagnosed precancerous stomach mucosa lesion, associated with increased risk of gastric cancer (GC).
- Operative Link on Gastric Intestinal Metaplasia (OLGIM) has been used to risk-stratify patients with IM. The European Society of Gastrointestinal Endoscopy recommends repeated surveillance endoscopy in 3 years for patients with the high-risk IM (ie, OLGIM III–IV).
- However, clinical adoption of surveillance for IM remains low, due to the lack of supporting clinical evidence from large prospective studies, as well as heterogenous gastric mucosal sampling and reporting practices.

What are the new findings?

- Standardised gastric mucosal mapping and OLGIM reporting enables risk stratification.
- Patients with OLGIM III–IV are at high risk of early gastric neoplasia (EGN), with greater than half (n=4/7) of EGNs attributed to high-risk IM occurring within 2 years (median 22.7 months, range 12.7–44.8 months).
- Patients with OLGIM III–IV, without history of *H. pylori* infection, demonstrate elevated serum trefoil factor 3 (TFF3) levels.
- Patients with OLGIM II are now identified to be at intermediate risk of EGN. This group accounts for one-quarter of the subsequent EGN cases in our study. Patients with OLGIM II would benefit from endoscopic surveillance.
- A significant smoking history (≥20 pack years) increases the risk of EGN among patients with intermediate-risk and high-risk IM (ie, OLGIM II–IV).

INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer and the third leading cause of cancer-related deaths in the world.[1] The high mortality is mainly due to

Significance of this study

How might it impact on clinical practice in the foreseeable future?

- Patients with OLGIM II–IV who are smoking should be counselled for smoking cessation.
- Patients with negative HP serology and high TFF3 warrant a high clinical suspicion of OLGIM III–IV.
- Risk stratification through OLGIM may offer an option of prioritising high-risk patients (OLGIM III–IV) for early endoscopic surveillance in 2 years, intermediate-risk patients (OLGIM II) for endoscopy in 5 years, while majority of the patients who are low risk OLGIM (OLGIM 0–I) may not require routine surveillance endoscopy.
- Risk stratification through OLGIM will help to optimise the cost-effectiveness of GC screening, particularly in regions with low-intermediate incidences of GC, through targeted endoscopic surveillance.
- Our findings hope to enhance awareness of risk and encourage the clinical adoption of standardised gastric mucosal sampling and OLGIM histological reporting.

late presentation of the disease. More than 70% of countries report a high mortality-to-incidence ratio (>0.8) for GC.[2 3] Only Japan and South Korea, both with government-sponsored endoscopic screening programmes, report low mortality-to-incidence ratios (0.43 and 0.35, respectively), highlighting the benefit of population endoscopic screening for early detection of GC.[3 4] The cost-effectiveness of GC screening is largely determined by the region's incidence of GC and cost of endoscopy. Population-wide endoscopic screening approaches in countries with intermediate or low incidence of GC, is not cost-effective.[2 5] For such regions, targeted endoscopic screening of high-risk individuals might be a better approach.[5] Risk stratification would therefore be an appropriate strategy to guide endoscopic screening.

The prevalent subtype (intestinal) of GC develops through a sequence of recognisable precancerous stages—inflammation, atrophy, intestinal metaplasia (IM), dysplasia and subsequent carcinoma.[6] Surveillance of patients with such precancerous stages may lead to early diagnosis of GC, and thus improved survival.[7–9] Premalignant gastric lesions are commonly found in everyday practice, and the European Society of Gastrointestinal Endoscopy has recommended endoscopic surveillance for premalignant gastric lesions.[9] However, clinical adoption of surveillance for premalignant gastric lesions remains low, largely due to the lack of supporting clinical evidence from large prospective studies, heterogenous sampling and reporting practices, as well as the cost of implementing population-level screening.

To ensure uniform reporting of such premalignant gastric lesions, the Operative Link of Gastritis Assessment (OLGA) was introduced.[10–12] Multiple studies have shown OLGA reliably identifies a subpopulation of patients (OLGA stage III–IV) with high risk of GC.[12 13] However, OLGA is based on the histological parameters of gastric atrophy, for which there is poor interobserver agreement. Others have advocated using IM in place of gastric atrophy through the Operative Link on Gastric Intestinal Metaplasia (OLGIM). In contrast to OLGA, OLGIM reports a high level of interobserver concordance, and categorises fewer patients to the high-risk stages of III and IV.[14 15] More studies are required to validate OLGIM and support its clinical adoption.[9]

The aim of this prospective study was developed to investigate the incidence of early gastric neoplasia (EGN) among participants with IM, and validate the utility of OLGIM for risk stratification of participants with IM.

METHODS

Study population

The Singapore Gastric Cancer Epidemiology and Molecular Genetics Programme (GCEP) is a prospective, multicentre cohort study. Singapore is a country with intermediate incidence of GC, where the incidence of GC is 18.6 and 12.3 per 100 000 population for men and women, respectively.[16] Participants were recruited from four major public hospitals in Singapore, which together provided 80% of the hospitalisation and specialist services in Singapore. Participants were eligible if: (i) they were of Chinese ethnicity; (ii) aged 50 years and above or (iii) had history of *H. pylori* (HP) infection and/or known premalignant gastric lesions such as atrophic gastritis and IM. Chinese individuals were selected because they have a higher incidence of GC than Malays or Indians in Singapore, where the age-standardised incidence is 25.7, 8.4, 6.6 per 100 000 population in Chinese, Indian and Malay men, respectively.[5 17] Exclusion criteria for this study included any severe acute or chronic medical, psychiatric condition or laboratory abnormality that may suggest the participant had an increased risk of undergoing routine endoscopy.

Participants and follow-up

From January 2004 through December 2010, a total of 4085 individuals were referred to GCEP (online supplemental appendix S1), of which 2980 underwent index endoscopy and subsequently completed 7541 endoscopies, whereby the average endoscopic surveillance period per participant was 4.4 (SD 1.2) years. At the end of the study, 2436 participants (82%) had completed 5 years of follow-up. Of the 543 participants who did not complete 5 years of follow-up, 366 withdrew from the study voluntarily, 118 developed medical conditions which rendered them unable to continue with regular endoscopic surveillance, 56 passed away due to causes unrelated to GC, 3 were diagnosed with EGN at baseline and 1 was diagnosed with EGN <12 months from the index endoscopy. Participants who did not complete 5 years of endoscopic surveillance were matched against the National Registry of Diseases Office for missed diagnoses of GC and we found one case of GC diagnosed 7 years after index endoscopy.

Endoscopy surveillance protocol

All endoscopic examinations were conducted by board-certified gastroenterologists and gastrointestinal surgeons using high quality white light endoscopy with rapid escalation to high-resolution image-enhanced endoscopy on detection of abnormal pathology. The examination protocol was systematic with detailed photographic documentation. Endoscopy was performed with local anaesthetic throat spray and all patients were offered conscious sedation with intravenous midazolam 1–2 mg to improve tolerance and thereby facilitate better visualisation of the gastric mucosa during the examination. Procedures were recorded on video for further validation and comparison. Participants who had never had an endoscopy or who had an endoscopy performed more than 12 months before enrolment underwent a prospective baseline endoscopy. After the baseline endoscopy, participants were scheduled for surveillance endoscopies at years 3 and 5. Two subgroups of participants had additional surveillance endoscopies. They are: (i) participants who had three or more risk factors (ie, those with IM, atrophic gastritis, family history of GC, presence of HP infection and

current or past history of smoking) were scheduled for additional endoscopies at year 1 and (ii) the initial 200 participants enrolled had an additional surveillance endoscopy at year 7.

Biopsy collection and histological reporting

Six biopsies consisting of two each from the antrum and corpus, one from the incisura (in accordance to the updated Sydney System for classification and grading of gastritis) and one from the cardia, were taken for histology examination (online supplemental appendix S2). Another biopsy from the antrum was taken for HP culture and genotyping. For this study, all histological specimens were centralised to a single histopathological laboratory. Two senior pathologists (TM and MS-T) agreed on the scoring systems and trained themselves for interobserver concordance with the first 200 cases of the study. Following this, other pathologists involved in the central review were also put through the same training process. All biopsy samples were assessed by two pathologists independently for HP infection, chronic gastritis, atrophic gastritis, IM and dysplasia. Interobserver agreement was subsequently re-evaluated in a subset of 525 biopsies between the two key pathologists who read majority of the specimens (TM and SS). The overall agreement (kappa value) between these two pathologists was 0.96 (95% CI 0.98 to 0.94).

Severity of gastritis and IM was scored on H&E staining using the updated Sydney System classification.[18] Of note, gastric atrophy, in this study, is defined as the loss or appropriate glands with the replacement by metaplastic intestinal glands. OLGIM stage was calculated based on the average percentage of IM representation in the antrum or corpus (online supplemental appendix S2).[14 19] Gastric tissue samples with ≥30% IM present underwent immunohistochemistry staining for mucins (MUC1, MUC2 and MUC5AC) to determine complete and incomplete IM subtypes.[20] Dysplasia was graded by the revised Vienna classification and typing of carcinoma was done according to the WHO classification of tumours.[21 22] Staging of adenocarcinoma (other than stage 0) was done according to the American Joint Committee on Cancer Staging Manual, Eighth Edition.[23]

Other procedures

Participants contributed blood samples, and completed a medical history interview with trained nurses at baseline. The blood samples acquired at baseline were assayed for levels of HP antibodies (Helico Blot 2.1 Western Blot Assay, MP Biomedicals Asia Pacific, Singapore)[24] and pepsinogens (E-Plate 'Eiken' Pepsinogen I and II, Tokyo, Japan). A positive pepsinogen index was defined as having both serum pepsinogen I ≤70 ng/mL and serum pepsinogen I/II ratio ≤3.0.[25 26] Patient serum levels of trefoil factor 3 (TFF3) and macrophage migration inhibitory factor 1 (MIF1) were measured using Quantikine Colourimetric ELISA kits (R&D Systems, Massachusetts, USA).[27–29] All serum samples were diluted by manual pipetting while the rest of the assay was performed on an automated system (Evolis 4 Plate Complete System, Biorad, California, USA), according to the manufacturer's protocols. The dilution factors for TFF3 and MIF1 used were 1:50 and 1:10, respectively.

All participants were followed up annually, either at the clinic or via telephone for symptom review in the years that they were not scheduled for endoscopy surveillance. All data captured were entered directly from source documents into electronic case report forms using the CLINTRIAL (Oracle Corporation) and REDCap web-based systems (Harvard Catalyst).

Outcomes

The primary endpoint of this study was defined as EGN, which included histological diagnosis of high-grade dysplasia, and adenocarcinoma.

A priori power calculation using discrete Cox's proportional hazard regression for this study estimated a sample size of 3000 participants, accounting for 10% attrition, with 80% power, $\alpha=0.05$, to detect an HR >2.5 with a 0.5% incidence, to an HR of >4.5 for an exposure with 0.25% incidence of EGN.

Statistical analysis

The incidence rate of EGN was calculated by dividing the number of EGN detected during the surveillance period by total person-years. The age-standardised incidence rates were calculated as the weighted average of the age-specific incidence rates per 100 000 person-years, whereby the weights are calculated on the basis of data from the Singapore 2010 population census report.[30]

Cox regression analysis was used to compare time-to-event EGN between patients with IM and those without. Proportional hazard assumption was assessed by both Schoenfeld residuals and the global goodness-to-fit test. Cumulative incidences were used to show event risk. Participants with at least one surveillance endoscopy after the baseline endoscopy (n=2736) were included in Cox regression analysis. Patients with EGN within 12 months from the index endoscopy was excluded from the Cox regression analysis. Established risk factors for GC such as older age, male sex, lower socioeconomic status, prior HP infection, family history of GC and previous gastric ulcers, were included in the subgroup analysis and interaction terms in the Cox regression models were used to test for heterogeneity of effect between subgroups.

All statistical analyses were performed using the R V.3.5.0 (R Core Team, 2018), the survival (V.3.1.11; Therneau, 2020) and the tidyverse (V.1.3.0; Wickham, 2019) packages.[31–33] All p values were two-sided, and those that were less than 0.05 were considered statistically significant.

RESULTS

Characteristics of patients in the GCEP cohort

Among the 2980 participants in the GCEP cohort, 1321 (n=44.3%) were found to have gastric IM. The baseline characteristics of patients in the GCEP cohort are detailed in table 1. The mean age was 59.1 years (SD ±6.7 years); 1541 were men (51.7%); 47.8% had a medical history of HP infection; 22.2% were current or previous smokers and 14.2% had a positive family history of GC. Majority of participants in our cohort with prior exposure to HP were successfully eradicated (97.1%). Of note, one of the 41 participants with non-eradicated HP was subsequently found to have EGN.

Patients with EGN

There was no late stage GC detected within GCEP. A total of 21 EGNs (13 high-grade dysplasia, 8 stage IA/IB gastric adenocarcinomas) were identified. Of these, three were detected at baseline, one occurred less than 12 months from the index endoscopy. Among the three cases without IM at baseline, two were found to have IM in subsequent endoscopies. Only the patient with diffuse subtype adenocarcinoma was not found to have IM. The median time to develop high-grade dysplasia and stage I adenocarcinoma was 22.7 (range, 12.2–48.1) and 28.1 (12.7–73.3) months, respectively. All cases of EGN within GCEP received early intervention: 6 underwent surgical resection (subtotal or

Table 1 Baseline demographic characteristics of 2980 participants from the Singapore Gastric Cancer Epidemiology and Molecular Genetics Programme, with the corresponding adjusted HR for subsequent early gastric neoplastic (EGN)

Risk factors	Proportion/mean	Multivariate adjusted HR* (95% CI)	P value
Early gastric neoplasia (EGN)	21 (0.7%)		
Age (years)			
Mean age	59.5±6.9	1.08 (1.02 to 1.16)	0.02
Gender			
Female	1439 (48.3%)		
Male	1541 (51.7%)		
Low SES†			
No	2245 (75.3%)	1.00	
Yes	735 (24.7%)	1.79 (0.85 to 8.48)	0.26
Smoking (pack years)‡			
0	2318 (77.8%)	1.00	
0–20	375 (12.6%)	1.72 (0.48 to 6.20)	0.41
≥20	287 (9.6%)	2.26 (0.63 to 8.19)	0.21
Alcohol consumption			
Absent	2471 (82.9%)	1.00	
Present	465 (15.6%)	2.69 (0.85 to 8.48)	0.09
First-degree family history of GC			
Absent	2558 (85.8%)		
Present	422 (14.2%)		
History of HP infection			
Absent	1557 (52.2%)	1.00	
Present	1423 (47.8%)	2.45 (0.86 to 6.99)	0.09
History of gastric ulcer			
Absent	2545 (85.4%)	1.00	
Present	435 (14.6%)	2.05 (0.71 to 5.96)	0.19
Serum pepsinogen index			
Negative	2521 (93.5%)	1.00	
Positive	175 (6.5%)	4.23 (1.34 to 13.37)	0.01
Atrophic gastritis			
Absent	2286 (76.7%)	1.00	
Present	694 (23.3%)	2.69 (1.03 to 7.06)	0.04
Intestinal metaplasia (IM)			
Absent	1659 (55.7%)	1.00	
Present	1321 (44.3%)	5.36 (1.51 to 19.02)	<0.01
OLGIM score			
No IM	1659 (55.7%)	1.00	
OLGIM I	506 (30.4%)	1.95 (0.39 to 9.74)	0.52
OLGIM II	252 (8.5%)	7.34 (1.60 to 33.7)	0.01
OLGIM III–IV	163 (5.4%)	20.77 (5.04 to 85.6)	<0.01

*Risk factors with p value <0.15 were included in the multivariate regression model to calculate the adjusted HR and were adjusted for age, low socioeconomic status (SES) and smoking. Patients with subsequent EGN within 12 months from the index endoscopy was excluded from the Cox regression analysis.
†Low SES is defined as the person has either low education level (primary or below) or the monthly income is below S$1500.
‡The amount of smoking in pack years, which is the number of packs of cigarettes smoked per day multiplied by the number of years of smoking.
GC, gastric cancer; HP, *H. pylori*; OLGIM, Operative Link on Gastric Intestinal Metaplasia.

total gastrectomy) and 10 underwent endoscopic curative resection. The remaining five participants had small lesions of high-grade dysplasia removed on detection. Among these five, two recurred at the same site of the initial resection 2 years (stage IA gastric adenocarcinoma) and 3 years (high grade dysplasia) later, respectively. The former had the adenocarcinoma removed via endoscopic submucosal dissection, while the latter had a curative endoscopic mucosal resection. The other three participants were followed up with endoscopic surveillance for 4–7 years, with no subsequent EGN identified. All but one participant with EGN were alive at the end of the study period. The participant passed away due to sepsis secondary to acute pyelonephritis 4 years after treatment of his high-grade dysplasia. Further details of these 21 participants are provided in table 2.

Predictive risk factors of EGN

Univariate and multivariate analyses were performed for each risk factor. Multivariate cox regression analysis showed that older age (adjusted-HR 1.08; 95% CI 1.02 to 1.16; p=0.02), positive serum pepsinogen index (adjusted-HR 4.23; 95% CI 1.34 to 13.37; p=0.01) and the presence of either atrophic gastritis (adjusted-HR 2.69; 95% CI 1.03 to 7.06; p=0.04) or gastric IM (adjusted-HR 5.36; 95% CI 1.51 to 19.0; p<0.01) were significant risk factors for EGN. A comprehensive analysis of all patient variables, reporting both univariate and multivariate cox regression analysis results, is provided in online supplemental appendix S3.

Risk stratification of gastric IM

Gastric IM was strongly associated with EGN and was concomitantly present in almost all EGN cases (n=18/21, 85.7%). The age-adjusted EGN incidence rates for participants with and without IM were 133.9 and 12.5 per 100 000 person-years, respectively. Patients with IM were further stratified using OLGIM staging, whereby the distribution of OLGIM I, II and III–IV were 68.6%, 19.1% and 12.3%, respectively (figure 1A). There was an increasing trend of EGN risk with higher OLGIM stages, whereby the age-adjusted EGN rates with OLGIM I, II and III–IV were 21.5, 108.8, 543.8 per 100 000 person-years, respectively (figure 1A). Participants with OLGIM stages III–IV lesions also had shorter time intervals between baseline endoscopy and subsequent EGN (median 22.7 months; range 12.7–44.8 months) compared with those with OLGIM stage II lesions (median 50.7 months; range 28.5–73.3 months; p=0.01) (figure 1B).

Characterising high-risk IM (OLGIM II–IV) and intermediate-risk IM (OLGIM II)

Patients with OLGIM II–IV were of older age, with a higher proportion of patients who were of lower socioeconomic status, smoked ≥20 pack years, have family history of GC, prior HP exposure and medical history of gastric ulcers (table 3). Patients with baseline OLGIM II–IV remained at significant risk of EGN (adjusted-HR 9.92; 95% CI 3.55 to 27.7; p<0.01), even after adjusting for the above differential patient covariates. There was also no evidence of any established risk factors of GC (ie, age, sex, lower socioeconomic status, smoking, family history of GC, previous HP exposure or history of gastric ulcers) posing as a significant modifier of the risk of EGN progression for OLGIM II–IV, compared with OLGIM 0–I (online supplemental appendix S4).

Patients with OLGIM II–IV could be further risk-stratified through smoking history and histological subtyping. OLGIM II–IV patients with a smoking history of ≥20 pack-years were associated with increased risk of EGN (HR 3.69; 95% CI 1.03 to 13.2; p=0.045) (online supplemental appendix S5A). OLGIM II–IV patients with incomplete IM (227/364, 62.3%)

Table 2 Demographic characteristics of the 21 participants within Singapore Gastric Cancer Epidemiology and Molecular Genetics Programme who developed early gastric neoplasia (EGN)

SN	Time to event from index gastroscopy (months)	EGN diagnosis (Stage)	EGN resection modality	Baseline atrophic gastritis	Baseline OLGIM	Baseline GIM subtype	Age at index endoscopy	Gender	Low SES	Alcohol consumption	Smoking (pack years)	First-degree relative with GC	History of HP infection	History of peptic ulcer disease	Serum pepsinogen ratio	Serum TFF3	Serum MIF
1	0.0	High grade dysplasia	EMR	Present	OLGIM II	Complete	75.0	Male	Yes	Present	0–20	No	Absent	Gastric ulcer	0.52	16.6	14.5
2	0.0	High grade dysplasia	Subtotal Gastrectomy	Present	OLGIM IV	Incomplete	72.0	Male	Yes	Absent	>20	No	Absent	Absent	4.11	7.1	63.2
3	0.0	High grade dysplasia	Subtotal Gastrectomy	Present	OLGIM II	Incomplete	58.0	Male	No	Present	>20	Yes	Present	Gastric ulcer	3.68	7.1	22.0
4	6.0	High grade dysplasia	None	Present	OLGIM III	Incomplete	59.0	Male	Yes	Absent	>20	No	Present	Duodenal ulcer	8.33	16.4	41.3
5	12.2	High grade dysplasia	None	Absent	Absent		50.0	Female	No	Absent	0	No	Present	Absent	5.68	6.1	22.9
6	12.7	Intestinal adenocarcinoma (stage IA)	Total gastrectomy	Absent	OLGIM III	Incomplete	57.0	Male	Yes	Present	>20	No	Present	Absent	5.55	9.2	27.8
7	13.6	Diffuse adenocarcinoma (stage IB)	Subtotal gastrectomy	Absent	Absent		55.0	Female	No	Absent	0	No	Present	Gastric ulcer	3.71	3.6	15.3
8	14.9	High grade dysplasia	ESD	Present	OLGIM III	Incomplete	51.0	Male	No	Absent	0	No	Present	Absent	4.43	5.5	56.9
9	16.6	Intestinal adenocarcinoma (stage IA)	Total gastrectomy	Absent	OLGIM I		68.0	Male	Yes	Absent	0	No	Present	Absent	3.72	5.8	42.9
10	17.4	High grade dysplasia	ESD	Present	OLGIM III	Incomplete	77.0	Female	Yes	Absent	0	No	Absent	Gastric ulcer	7.76	10.5	23.6
11	18.7	High grade dysplasia	None	Absent	Absent		66.0	Female	Yes	Absent	0	No	Absent	Gastric ulcer	0.44	13.7	52.8
12	22.7	High grade dysplasia	ESD	Absent	OLGIM III	Incomplete	74.0	Female	Yes	Absent	0	Yes	Present	Absent	5.86	10.0	14.4
13	24.4	High grade dysplasia	EMR	Absent	OLGIM I		69.0	Male	No	Absent	0–20	No	Absent	Absent	0.12	12.8	16.1
14	24.6	High grade dysplasia	None	Present	OLGIM IV	Incomplete	75.0	Male	Yes	Absent	0–20	No	Absent	Absent	2.27	7.6	20.2
15	27.7	Intestinal adenocarcinoma (stage IB)	Total gastrectomy	Present	OLGIM IV	Incomplete	51.0	Male	No	Present	0–20	No	Absent	Absent	4.10	5.8	22.3
16	28.5	Intestinal adenocarcinoma (stage IA)	ESD	Present	OLGIM II	Incomplete	59.0	Male	No	Present	>20	No	Present	Gastric ulcer	2.71	4.6	14.0
17	44.8	High grade dysplasia	EMR	Present	OLGIM III	Incomplete	69.0	Male	No	Present	0	No	Present	Absent	8.97	4.7	11.2
18	48.1	High grade dysplasia	EMR	Absent	OLGIM I		62.0	Male	No	Present	0	No	Present	Gastric ulcer	8.00	3.9	30.6
19	50.7	Intestinal adenocarcinoma (stage IA)	ESD	Present	OLGIM II	Incomplete	72.0	Female	Yes	Absent	0	No	Present	Absent	2.48	5.1	86.9
20	50.7	Intestinal adenocarcinoma (stage IA)	ESD	Absent	OLGIM II	Complete	60.0	Male	No	Present	>20	No	Present	Absent	7.68	16.5	18.6
21	73.3	Intestinal adenocarcinoma (stage IA)	ESD	Present	OLGIM II	Incomplete	67.0	Female	No	Absent	0	Yes	Present (non-eradicated)	Absent	5.20	9.8	20.0

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; GC, gastric cancer; MIF, macrophage migration inhibitory factor; OLGIM, Operative Link on Gastric Intestinal Metaplasia; SES, socioeconomic status; TFF3, trefoil factor 3.

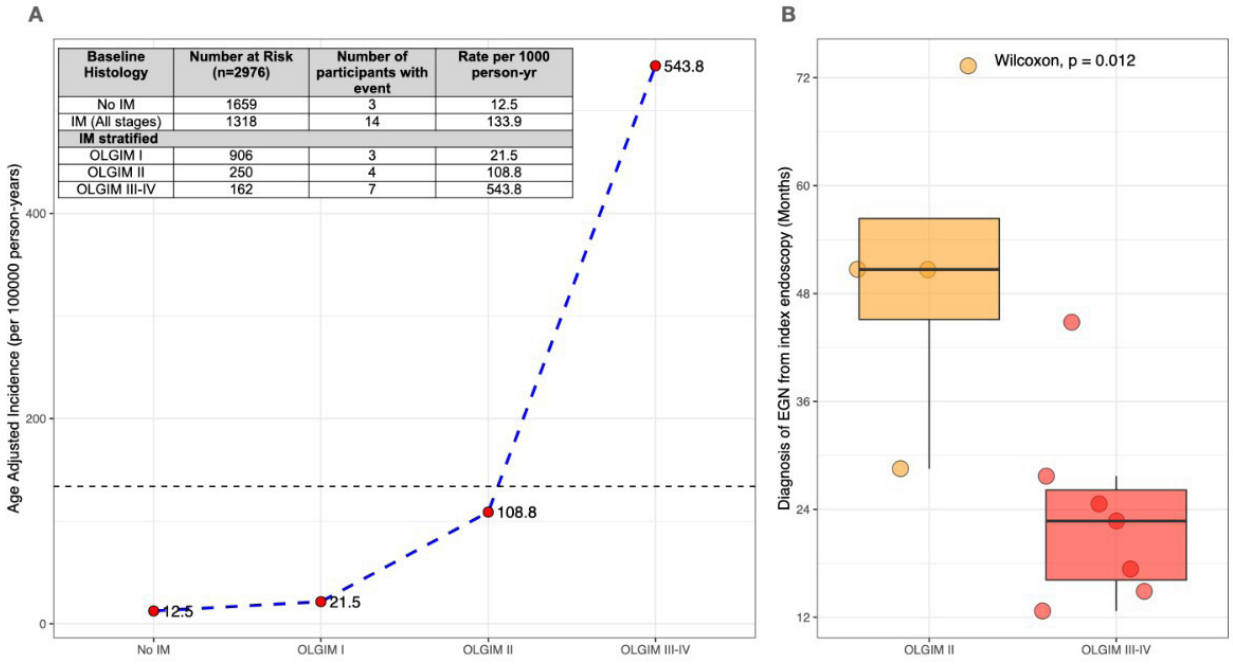

Figure 1 (A) Age-adjusted early gastric neoplasia (EGN) incidence rates stratified by baseline Operative Link on Gastric Intestinal Metaplasia (OLGIM) stages. (B) Box plot depicting the time (years) to develop EGN among patients with OLGIM II (orange) and OLGIM III–IV (red), with respective median time (midline) of 50.7 months (range 28.5–73.3) and 22.7 months (range 12.7–44.8). The 25th and 75th quartile are represented by the lower and upper end of the boxes. IM, intestinal metaplasia.

were at also at increased risk of EGN, compared with those with complete IM (137/364, 37.6%), although the difference was not statistically significant (HR 5.96; 95% CI, 0.77 to 46.4; p=0.09) (online supplemental appendix S5B).

To identify potential biomarkers for high-risk OLGIM, we tested three serum biomarkers, TFF3, MIF and pepsinogen II/I ratio. All three biomarkers demonstrated a gradational trend with increasing OLGIM stage (figure 2A), while both MIF and the pepsinogen ratio decreased with increasing OLGIM stage, and TFF3 levels increased with more severe IM stages. However, only serum TFF3 was able to accurately discriminate between OLGIM III–IV and OLGIM 0–II gastric lesions among patients who tested negative for HP (AUROC 0.749; 95% CI 0.628 to 0.870; p<0.01) (figure 2B).

Transition states of gastric IM

We investigated the transition states of patients with IM as shown in figure 3, whereby we categorised the change in OLGIM stages over 5 years as either (i) reversal, (ii) low risk, (iii) intermediate risk or (iv) high risk, defined by the subsequent OLGIM stage at the end of the study (figure 3A). With increasing OLGIM stages, the proportion of patients who subsequently achieve IM reversal (ie, subsequently no IM or regress to OLGIM I) decreases (figure 3B). Of note, there were no patients with baseline OLGIM III–IV who achieved IM reversal. Conversely, only a small proportion of patients with baseline OLGIM I, subsequently develop OLGIM II (10%) and OLGIM III–IV (3%). Serum pepsinogen index was a significant predictor of OLGIM I progression to OLGIM II–IV in these cases; participants with OLGIM stage I lesions with positive serum pepsinogen index were twice more likely to progress to higher stages (OR 5.81; 95% CI 2.26 to 14.9; p<0.01) (online supplemental appendix S6).

DISCUSSION

Although there is a strong recommendation from the European Society of Gastrointestinal Endoscopy that patients with advanced IM (OLGIM III–IV) should undergo endoscopic surveillance, the clinical adoption of endoscopic surveillance of gastric IM remains low, due to the lack of supporting clinical evidence from large prospective studies, as well as heterogenous gastric mucosal sampling and reporting practices. Risk stratification of target populations for endoscopic surveillance may bring potential advantages. In countries with low-intermediate incidences of GC, prioritised endoscopic surveillance through OLGIM risk stratification may enhance the early detection of GC, prompt therapeutic intervention and lower GC mortality rates.

This study reaffirms that patients with IM are at risk of EGN.[34] However, the risk of EGN is most evident in participants with OLGIM stages II–IV, representing one-third (31.4%) of participants with IM. The increase in risk of EGN with advanced OLGIM stages reaffirms severe grade and extensive spread of IM as key predictors of its neoplastic progression. Previously, only OLGIM III–IV were reported as high-risk states targeted for surveillance endoscopy,[35 36] with recommended endoscopic surveillance in 3 years.[9] Here, we show that OLGIM stage II also carries significant risk of EGN, although in these cases, the progression to EGN took longer time (median 50.7 months; range 28.5–73.3 months), compared with lesions of OLGIM stages III to IV (median 22.7 months; range 12.7–44.8 months). Our findings thereby suggest that patients with OLGIM stages III–IV could benefit from earlier repeat surveillance endoscopy in 2 years, and patients with OLGIM stage II lesions could benefit from a repeat surveillance endoscopy in 4–5 years. Using absolute risk reduction analysis, the minimal number of patients required to detect one EGN through two yearly regular endoscopic surveillance among those with OLGIM stages I, II and III–IV were 485, 60 and 18, respectively.

Table 3 Differential characteristics of patients with high risk IM (ie, OLGIM II–IV)

Factors	No IM (N=1659)	OLGIM I (N=906)	OLGIM II–IV (N=415)	P value
Early gastric neoplasia (EGN)	3 (0.2)	3 (0.2)	15 (3.6)	<0.001
Age (years)				
Mean age	58.2±6.3	60.5±7	62.0±7.4	<0.001
Gender				
Female	791 (47.7)	455 (50.2)	193 (46.5)	0.345
Male	868 (52.3)	451 (49.8)	222 (53.5)	
Low SES*				
No	1318 (79.4)	651 (71.9)	276 (66.5)	<0.001
Yes	341 (20.6)	255 (28.1)	139 (33.5)	
Smoking (pack years)†				
0	1311 (79.0)	710 (78.4)	297 (71.6)	0.01
0–20	194 (11.7)	119 (13.1)	62 (14.9)	
≥20	154 (9.3)	77 (8.5)	56 (13.5)	
Alcohol consumption				
Absent	1386 (83.5)	760 (83.9)	325 (78.3)	0.101
Present	249 (15.0)	135 (14.9)	81 (19.5)	
First-degree family history of GC				
Absent	1423 (85.8)	793 (87.5)	342 (82.4)	0.046
Present	236 (14.2)	113 (12.5)	73 (17.6)	
History of HP infection				
Absent	1042 (62.8)	378 (41.7)	137 (33.0)	<0.001
Present	617 (37.2)	528 (58.3)	278 (67.0)	
History of gastric ulcer				
Absent	1460 (88.0)	750 (82.8)	335 (80.7)	<0.001
Present	199 (12.0)	156 (17.2)	80 (19.3)	
Atrophic gastritis				
Absent	1509 (91.0)	616 (68.0)	161 (38.8)	<0.001
Present	150 (9.0)	290 (32.0)	254 (61.2)	

*Low socioeconomic status (SES) is defined as the person has either low education level (primary or below) or the monthly income is below S$1500.
†The amount of smoking in pack years, which is the number of packs of cigarettes smoked per day multiplied by the number of years of smoking.
GC, gastric cancer; HP, *H. pylori*; IM, intestinal metaplasia; OLGIM, Operative Link on Gastric Intestinal Metaplasia.

Among the participants with IM, the majority (67.1%) were found to have low-risk stage IM (OLGIM stage I). We believe we are the first to report a large cohort of such participants, with prospective endoscopic examination and standardised biopsies for histopathology comparison, to demonstrate that participants with OLGIM stage I lesions do not have significantly increased risk of EGN, compared with participants without IM. This finding reaffirms the conclusion by some earlier studies that the majority of IM lesions are benign, and do not warrant surveillance endoscopy.[9 37] However, our study also identified a significant subset of participants (12.3%) with OLGIM stage I lesions who did progress to OLGIM stages II–IV. This may represent a subset of patients to have elevated risk of EGN despite low-risk IM, whereby we found that those with positive serum pepsinogen index were twice more likely to progress.

Our study also observed a gradational drop in the proportion of patients whose OLGIM were down staged over 5 years; the IM reversal rates for patients with baseline OLGIM I, II and III–IV were 24.4%, 4.5% and 0, respectively. The low proportion of IM reversal rates among patients with baseline OLGIM II, coupled with the increased proportion of cases that progress to high-risk OLGIM (12.1%) and subsequent EGN strengthens the argument for OLGIM II endoscopic surveillance.

Incomplete IM has often been highlighted as a risk factor for EGN development.[38–40] In our study, the incomplete subtype carries an eightfold increased risk of developing EGN (n=546; OR 8.4; 95% CI 1.9 to 37.8; p=0.005) compared with complete subtype of IM among participants with mucin staining (online supplemental appendix S5D). In addition, the majority of participants (13/15) with IM developing EGN had the incomplete subtype of IM. It showed the incomplete subtype carries substantial clinical significance. However, we did not find the incomplete subtype a statistically significant independent risk factor for EGN among participants with OLGIM II–IV (HR 5.96; 95% CI 0.77 to 46.4; p=0.09). More prospective studies would be required to substantiate the notion that subtyping IM would offer additional prognostic value for patients with gastric lesions of OLGIM stages II–IV.

Our study group previously demonstrated that IM patients with shortened telomeres and somatic copy number alterations were associated with subsequent development of EGN, and conversely, patients exhibiting normal epigenomic patterns were associated with regression.[41] In this study, patients with OLGIM II–IV with ≥20 pack-years of smoking history were at increased risk of subsequent EGN, whereby there is an inverse trend between pack-years of smoking and telomere length.[42] Smoking is already a known risk factor associated with GC, and it has been demonstrated that the risk of GC among smokers would decrease to that of patients who never smoked 10 years after smoking cessation.[43] Our study findings highlight that smoking adds to risk of EGN among patients with high-risk IM, and suggest that these patients should be counselled for smoking cessation.

There are few reliable blood markers for detecting GC, and even fewer markers to diagnose high-risk IM. TFF3 protein have been shown to be absent from the pyloric mucosa, unless IM is present,[44] and thus previously investigated as a promising screening marker for EGN. Previous clinical cohorts have also demonstrated serum detection of TFF3 protein expression in patients with gastric IM.[45 46] Our study results demonstrate that high TFF3 measurements, particularly when associated with negative HP serological status, may identify patients with OLGIM III–IV, who are at higher risk of GC, to whom endoscopy should be offered.

In our study, we also found atrophic gastritis an important risk factor for EGN. Furthermore, risk assessment of extensive atrophy is also possible on endoscopic examination alone.[47] However, in our study, we noticed a discordance of atrophy and gastric IM, with lower prevalence of atrophic gastritis (24%) compared with that of gastric IM (43.1%). This is due to cases with few goblet cells present, which can be graded as mild IM, but yet without any stark atrophy present. Furthermore, among our patients with atrophy, we were unable to provide 6% of patients any further risk-stratification grading, as the full thickness mucosa was not present on histopathology for precise grading. In addition, the severity of atrophy in our study may understated as the pseudopyloric metaplasia resembles the antral glands. In brief, our experience comparing between histological gastric atrophy and gastric IM is consistent with previous workgroups who found poor interobserver agreement with atrophy, and thus we too advocate using IM in place of atrophy for uniform histological reporting.

GCEP is the first large, prospective longitudinal study to provide scheduled endoscopic screening and surveillance with standard biopsy protocol to a cohort of participants with a high prevalence (44%) of gastric IM. Despite screening participants at higher risk of EGN, our study only detected a small number

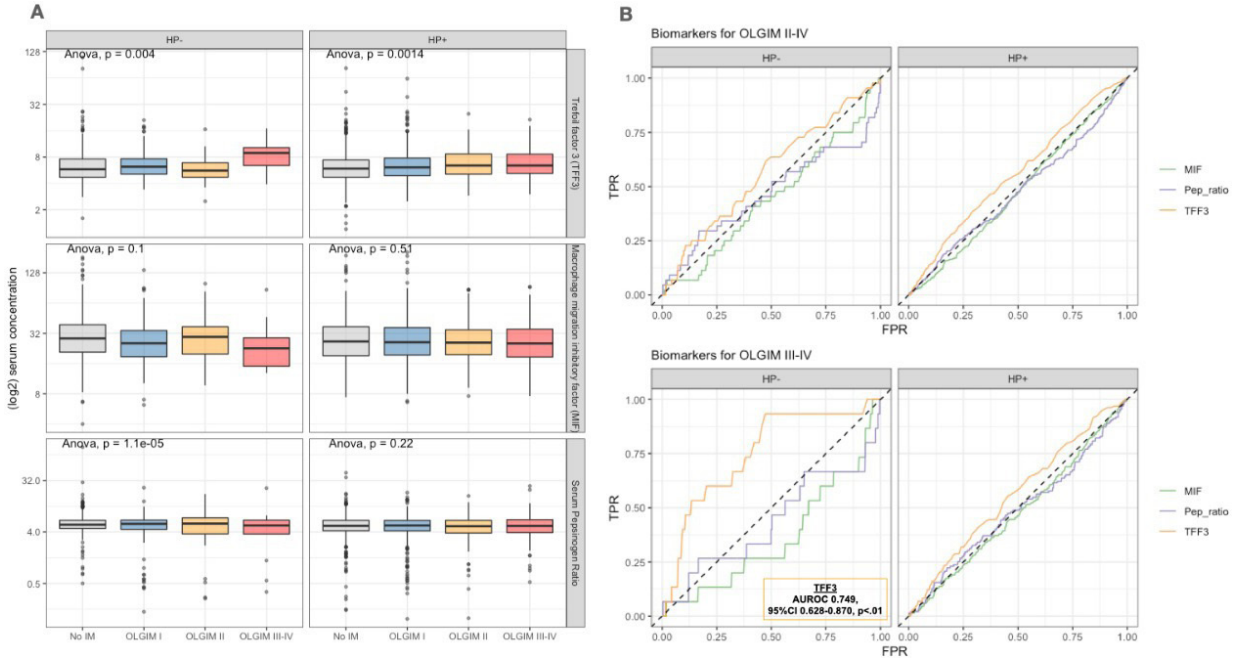

Figure 2 (A) Box plots of serum biomarkers concentrations (TFF3, MIF and pepsinogen I/II ratio) stratified by the negative status (HP–; left column) or positive status (HP+; right column) of HP serology across baseline OLGIM stages (x-axis). Serum concentrations are variance transformed using log2 units and statistical differences tested through ANOVA. (B) ROC diagrams of serum biomarkers (TFF3, MIF, Pepsinogen I/II ratio) stratified by stratified by the negative status (HP–; left column) or positive status (HP+; right column) of HP serology and the classification definitions of either (OLGIM II–IV vs OLGIM 0–I; top row) or (OLGIM III–IV vs OLGIM 0–II, bottom row).

ANOVA, analysis of variance; FPR, false positive rate; HP, *H. pylori*; IM, intestinal metaplasia; MIF, macrophage migration inhibitory factor; OLGIM, Operative Link on Gastric Intestinal Metaplasia; ROC, receiver operating characteristic; TFF3, trefoil factor 3; TPR, true positive rate.

of EGNs (n=21), which is consistent with the decreasing EGN incidence within the Singapore population during the time of study.[48] This low incidence of GC mirrors what is seen in many developed societies and reinforces the rationale for a risk-stratified approach. Furthermore, there are inherent selection biases within our study, which may affect the external validity of our findings, such as only including patients of Chinese ethnicity, and patients above 50 years old. For example, we did not find positive family history a significant risk factor for subsequent EGN. However, we still believe, that patients with positive family

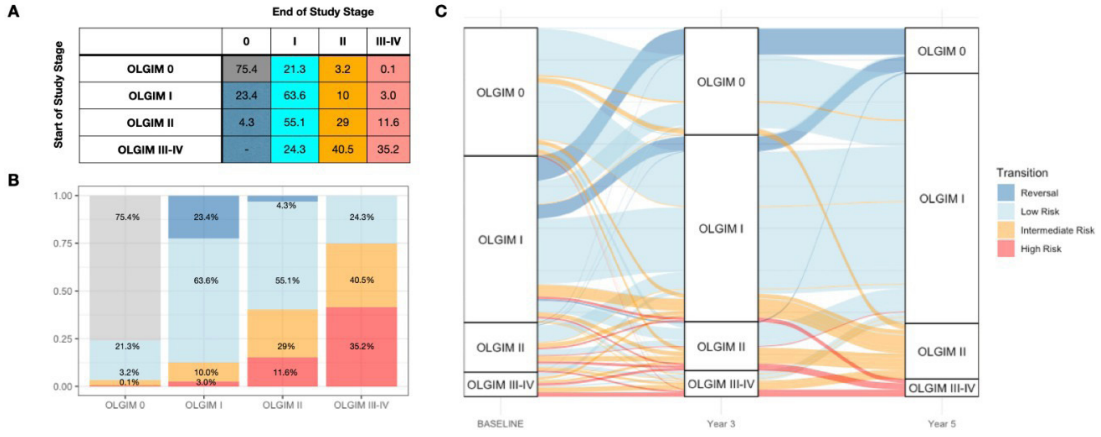

Figure 3 (A) Proportions of patients within Singapore Gastric Cancer Epidemiology and MolecularGenetics Programme (GCEP), stratified by baseline OLGIM stages (rows) and subsequent OLGIM stages (columns) at 5 years. Each cell represents the proportion (%) of patients of that baseline OLGIM stage with the corresponding end of study OLGIM stage. Cells are coloured to indicate transition states of no IM (grey), reversal (blue), low risk (light blue), intermediate risk (orange) and high risk (red). (B) Bar plot indicating the proportion (%) of patients from each baseline OLGIM stage (x-axis) with the resulting transition state: no IM (grey), reversal (blue), low risk (light blue), intermediate risk (orange) and high risk (red). (C) Alluvial flowchart diagram of patients within GCEP: only patients with gastric IM diagnosed in at least one endoscopy were included for this diagram. The flowchart follows each patients at baseline endoscopy (stratified by the OLGIM stage) and the patient's subsequent OLGIM stage at visit 3 and visit 5, whereby the patients trajectory summarised by the corresponding transition state trajectory: no IM (grey), reversal (blue), low risk (light blue), intermediate risk (orange) and high risk (red). IM, intestinal metaplasia; OLGIM, Operative Link on Gastric Intestinal Metaplasia.

history are at increased risk. This discordance may be attributed to GCEP only having recruited patients aged 50 years and above, while it was been previously reported that patients with one parent diagnosed with GC before 50 years of age, developed GC approximately 10 years earlier than individuals without a family history of GC.[49] Nonetheless, in GCEP extraordinary effort was undertaken to strengthen the validity of the outcome data. The use of standardised endoscopy protocols with stomach mapping biopsies was enforced through affirmation with video records. Participants were tele-interviewed annually to achieve a high compliance rate (81.8%) with scheduled endoscopies. Furthermore, all participants lost to endoscopic follow-up had their records matched with the National Registry of Disease Office. Detailed information on individual-level exposure were collected prospectively, thus limiting the concerns about temporality, differential classification, and recall bias.

CONCLUSION

In summary, the GCEP study cohort, set in a population with low-intermediate incidence of GC, showed that IM is prevalent and patients with IM are at increased risk of EGN. However, the majority of patients with IM, have a low-risk IM phenotype, and may not have neoplastic progression within 5 years. Yet, for a subset of patients with high-risk and intermediate-risk IM, timely endoscopic surveillance resulted in no late-stage GC. Our GCEP cohort findings suggest that risk stratification using OLGIM offers a feasible method of prioritising high-risk patients (OLGIM III–IV) for early endoscopy surveillance in 2 years and intermediate-risk patients (OLGIM II) for endoscopy in 5 years, while the vast majority of patients with no metaplasia or focal IM (OLGIM 0–I) may not require surveillance endoscopy. We hope our findings would enhance awareness of risk and encourage the clinical adoption of standardised gastric mucosal sampling and OLGIM histological reporting.

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