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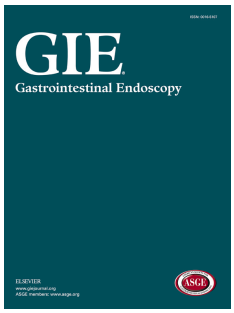

The endoscopists' biopsy rate as a quality indicator for outpatient gastroscopy: a multicenter cohort study with validation

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Title: **The endoscopists' biopsy rate as a quality indicator for outpatient gastroscopy: a multicenter cohort study with validation**

Short title: Biopsy rate as a gastroscopy quality marker

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Disclosures

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WJ and MFK conceived the idea of the study. WJ, MFK, PW, and JR contributed to the design of the research. PW was responsible for statistical analysis. WJ, MFK, JS,

RS, MR, AM, AB, and KK were involved in data collection and data analysis. All authors edited and approved the final version of the manuscript.

ABSTRACT

Background and Aims

The gastric premalignant conditions (GPCs) diagnosis rely on endoscopy with mucosal sampling. We hypothesized that the endoscopists' biopsy rate (EBR) might constitute a quality indicator for esophagogastroduodenoscopy (EGD) and we have analyzed its association with GPC detection and the rate of missed gastric cancers (GCs).

Methods

We analyzed EGD databases from 2 high-volume outpatient units. EBR values, defined as proportion of EGDs with ≥1 biopsy to all examinations, were calculated for each endoscopist in Unit A (derivation cohort) and divided by the quartile values into 4 groups. GPC detection was calculated for each group and compared using multivariate clustered logistic regression models. Unit B database was used for validation. All patients were followed with Cancer Registry for missed GCs, diagnosed between 1 month and 3 years after negative EGDs.

Results

Sixteen endoscopists in Unit A performed 17,490 EGDs of which 15,340 (87.7%) were analyzed. EBR quartile values were 22.4% to 36.7% (low EBR), 36.8% to 43.7% (moderate), 43.8% to 51.6% (high), and 51.7% and 65.8% (very-high); median value 43.8%. The moderate, high, and very high EBR groups' odds ratios of detecting GPC were 1.6 (95% CI, 1.3-1.9), 2.0 (95% CI, 1.7-2.4) and 2.5 (95% CI, 2.1-2.9), respectively, when compared with low EBR group (*P*<.001). This association was confirmed with the same thresholds in validation cohort.

Endoscopists with higher EBR (≥43.8%) had a lower risk of missed cancer as compared with lower EBR group (OR=0.44; 95% CI, 0.20-1.00; *P*=.049).

Conclusions

The EBR parameter is highly variable among endoscopists, associated with efficacy in GPC detection and the rate of missed GCs.

Keywords: Gastroscopy; Quality Indicators; Precancerous Conditions

INTRODUCTION

Gastric cancer (GC) usually presents at an advanced stage in the Western world with limited curative therapy opportunities. Despite a consistent decline in the global incidence and mortality of GC, it remains to be the fifth most common malignancy in the world and the third leading cause of cancer mortality (1). In 2015, there were 1.3 million incident cases and 819,000 deaths due to GC worldwide (2).

A significant proportion of these neoplasms arises from benign, precancerous conditions. For instance, the most common subtype of gastric cancer, a non-cardia intestinal-type adenocarcinoma, develops on a background of longstanding mucosal inflammation through a number of stages from chronic atrophic gastritis, by way of intestinal metaplasia, through low-grade and high-grade dysplasia, up to cancer. This sequence is known as Correa's cascade (3).

Esophagogastroduodenoscopy (EGD) with biopsies has a primary role in the diagnosis and surveillance of patients with gastric precancerous conditions (GPCs) and is considered to have a high sensitivity and specificity in cancer diagnosis.

However, despite growing experience in the field of endoscopy, a significant proportion of neoplastic lesions remain undetected. A recent meta-analysis has shown that 11.3% of upper gastrointestinal tract (UGI) cancers are missed at EGD up to 3 years before the diagnosis (4). These findings underscore the importance of quality control for this procedure.

In recent years, several guidelines and position statement papers on EGD quality have been published (5-7). Most of the presented measures, however, are based on low-quality evidence and are not associated with significant outcomes, such as neoplasia detection or interval cancer risk. Because the diagnosis of precancerous conditions and early cancers in conventional EGD relies on biopsy sampling of suspicious areas in the UGI tract we hypothesized that within a group of competent endoscopists the rate of obtaining biopsy specimens during endoscopy broadly reflects the number of detected abnormalities. We considered this as a potentially objective and reproducible quality marker for routine, outpatient EGD. Therefore, the aim of this study was to investigate the variability in taking biopsies by endoscopists and to analyze the association between a novel quality indicator, the endoscopists' biopsy rate (EBR), and detection of GPCs in the stomach and the rate of missed GCs.

METHODS

Study design

This was a multicenter, retrospective, cohort study analyzing outpatient EGD databases and histopathology reports from 2 high-volume, distinct geographically, endoscopy units between 2002 and 2015:

- Unit A – Endoscopy unit at the Department of Cancer Prevention, the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw.
- Unit B – Endoscopy unit by the Department of Gastroenterology, Pomeranian Medical University, Szczecin.

The database from Unit A was used as a derivation cohort to assess the EBR parameter and to analyze its correlation with GPC detection. Unit B database was used for external validation. Finally, both databases were used to find an association between EBR and the rate of missed cancers (detailed methodology explained below). The research proposal was reviewed and accepted by the ethics committee at the authors' institution on June 14, 2017 (49/PB/2017).

Endoscopists' biopsy rate (EBR) parameter

For each endoscopist, we counted biopsy rate (EBR) as a percentage of EGDs with at least one biopsy specimen obtained for histology from the esophagus, stomach, or the duodenum (ICD-9 codes 45.14, 45.16, 42.24) to all performed EGDs in the study period. Biopsies for rapid urease test were not included.

Derivation group (Unit A)

In the analysis, we have included full reports on subsequent adult patients undergoing diagnostic EGD, mostly for UGI symptoms evaluation. All endoscopists included in the study were staff specialists in internal medicine or gastroenterology, who underwent dedicated training in UGI endoscopy and were considered competent to perform diagnostic EGDs independently. Reports on juvenile patients (<18 years old) or with incomplete data were excluded, as well as EGDs performed by trainees

and endoscopists who did fewer than 100 procedures during the study period. Unit A database consisted of endoscopy reports including:

- Patients' data: personal identification number (PESEL), hospital number (PID), gender and date of birth.
- EGD data: indication, date, type of sedation, type (model) of the endoscope, examination report (descriptive), main gastroscopy findings, procedure ICD-9 code, number and description of containers used for histopathology specimens, and rapid urease test (if obtained).
- Endoscopist data: full name of endoscopist performing the procedure and assisting physician (if present).

All indications for EGD were coded and assigned into 4 groups: (1) symptoms evaluation (1a – benign symptoms 1b- alarm symptoms), (2) premalignant conditions surveillance, (3) cancer and nonepithelial neoplasms (known cancer, high suspicion of cancer in imaging tests, cancer during treatment, cancer follow-up), and (4) others. We linked EGDs with corresponding histopathology reports. Each histopathology finding was assigned to the esophagus, stomach, or duodenum and afterward characterized as a normal mucosa (no pathology in the microscopic examination), non-neoplastic lesions (eg, acute gastritis, fundic gland polyp, etc), precancerous condition (eg, atrophic gastritis, intestinal metaplasia, etc), cancer, or non-epithelial neoplasm (eg, neuroendocrine tumors, GISTs, lymphomas etc).

For each endoscopist we counted EBR values and then divided them by the quartile values into 4 groups, corresponding to low, moderate, high, and very-high EBR groups. We analyzed the association between EBR groups and detection of GPCs (atrophic gastritis, intestinal metaplasia, and dysplasia; low-, indefinite-, and

high-grade), and additionally detection of all UGI premalignant conditions including GPCs, but also Barrett's esophagus (BE), squamous intraepithelial neoplasm (SIN), and duodenal adenomas (DAs).

Validation group (Unit B)

The Unit B database constituted the validation cohort. For this database, we have used the same inclusion and exclusion criteria as for derivation cohort and coded endoscopy reports and histopathology findings in a similar fashion. This database, however, did not contain information on indications for EGD, type of the endoscope and sedation.

Missed cancers

We followed-up all patients from Unit A and Unit B using their personal identification numbers (PESEL) through the National Cancer Registry to identify those diagnosed with GC coded C.16 according to the International Classification of Diseases, 10th Revision – ICD 10 before the December 31, 2015. Missed cancers were defined as those diagnosed after 1 month and within 3 years after an EGD showing no evidence of cancer. We have used the same criteria for missed GCs as in several previous studies within the field (4,8-11). This definition is based on observatory studies by Fujita et al, (12) showing that a doubling time of gastric cancer on the mucosal surface is approximately 2 to 3 years. Therefore, an assumption is made, that cancers diagnosed within 3 years after negative gastroscopy were already present at the time of initial examination as either early malignancy or precursor lesion. Cancers diagnosed at the initial EGD (and within 1 month) were considered baseline cancers (we decided that 1 month should include

all cases of delayed histopathology results), and those diagnosed after 3 years were classified as latent cancers.

Statistical Methods

Baseline characteristics were prepared using medians, interquartile ranges, and contingency tables. Spearman correlation was used to measure the association between EBR and the risk of GPC and dysplasia at EGD. We analyzed the association between EBR groups and the detection of GPCs and all UGI premalignant conditions using multivariate clustered logistic regression models. Because one patient may have had more than one EGD, standard errors of model estimates were clustered according to patients to adjust for intrapatient correlation. We reported odds ratios (ORs) and 95% confidence intervals (CI) adjusted for patient's sex and age at the time of diagnosis. All statistical tests were 2-sided. *P* value of less than 0.05 was considered to indicate statistical significance. All analyses were performed with Stata software, version 13.1 (Stata Corporation, College Station, Tex, USA).

RESULTS

Derivation cohort

Unit A database consisted of 17,490 EGD reports on 13,875 patients, of which 2,150 (12.3%) met exclusion criteria and the remaining 15,340 (87.7%) were analyzed (12,433 patients). The study flowchart is presented in **Figure 1.** Most patients (10,503; 84.5%) had one EGD, 1,365 (11.0%) had 2 EGDs and 565 (4.5%) had 3 or more EGDs (maximum 14). In total, 1,331 (12.7%) GPCs were detected, including 188 diagnoses of gastric dysplasia (14.2%; any grade), 150 BE (1.0%), 16 SINs (0.1%) and 49 DAs (0.3%). The median patients' age was 57 years (range 18-

91 years) and the most common indication for EGD was an upper abdominal pain, accounting for 4379 procedures (28.5%). Most of the EGDs (n=8,976) were performed on female patients (58.5%). Nearly all procedures were performed with local anesthetic only (n=15,317, 99.8%) and with the use of standard video-endoscopes (93.6%). Detailed characteristics of Unit A cohort are presented in **Table 1**.

The EBR value of 16 endoscopists in this cohort varied between 22.4% and 65.8%. The median EBR value was 43.7% and the quartile values of EBR were as follows: 22.4% to 36.7% (low EBR group), 36.8% to 43.7% (moderate EBR group), 43.8% to 51.6% (high EBR group), and 51.7% to 65.8% (very-high EBR group), respectively. Endoscopists were assigned to each group (4 in each group). The moderate, high, and very-high EBR groups' ORs of detecting GPC were 1.6 (95% CI, 1.3-1.9; *P*<.001), 2.0 (95% CI, 1.7-2.4; *P*<.001) and 2.5 (95% CI, 2.1-2.9; *P*<.001), respectively, as compared with low EBR group. We performed additional analysis extracting only gastric dysplasia (GD) detection (any grade). For GD, the ORs were 2.1 (95% CI, 1.1-4.0; *P*=.024), 2.7 (95% CI, 1.5-4.7; *P*=.001) and 1.9 (95% CI, 1.1-3.4; *P*=.025), for the moderate, high, and very-high EBR group, respectively, when compared to low EBR group. Last, for all UGI premalignant conditions, the moderate, high, and very-high EBR groups' ORs were 1.6 (95% CI, 1.3 – 1.9; *P*<.001), 1.9 (95% CI, 1.6 – 2.2; *P*<.001) and 2.5 (95% CI, 2.1 – 2.9; *P*<.001), respectively, as compared with low EBR group.

Additionally, having indications for the EGDs, we have performed sensitivity analysis in which we have excluded all procedures with indications of previously recognized premalignant conditions, genetic cancer syndromes, cancer or high suspicion of cancer and nonepithelial neoplasms. This has excluded 4,690 EGDs

(26.8%) and the remaining 12,800 EGDs were analyzed. The association between EBR and GPC detection was maintained. The moderate, high and very high EBR group ORs for detecting GPC were 1.8 (95% CI, 1.4–2.2; *P*<.001), 2.2 (95% CI, 1.8–2.7; *P*<.001) and 3.2 (95% CI, 2.7–3.8; *P*<.001) and for GD detection it was 2.3 (95% CI, 1.1–4.8; *P*=.021), 2.8 (95% CI, 1.5–5.2; *P*=.002) and 2.1 (95% CI, 1.1–3.9; *P*=.026), respectively, as compared with low EBR group.

Validation cohort

Unit B database consisted of 14,589 EGD reports on 11,333 patients, of which 295 (2.0%) met exclusion criteria and the remaining 14,294 (98.0%) were analyzed. Most patients (9,425; 83.2%) had one EGD, 1,334 (11.8%) had 2 EGDs, and 574 (5.1%) had 3 or more EGDs (maximum 14). In total, 285 GPCs were detected, including 118 (0.8%) GD (any grade). The median patients' age was 56 (range 18-96). As in the derivation cohort, most of the EGDs (n=8,932) were performed on females (62.5%).

The EBR range of 10 endoscopists in Unit B varied between 22.0% and 52.9%. Using the EBR quartile ranges established in Unit A, we have assigned endoscopists from Unit B into 4 EBR groups and analyzed the ORs of GPC detection. The moderate, high, and very-high EBR groups' ORs of detecting GPCs were 0.8 (95% CI, 0.5-1.2), 3.0 (95% CI, 2.4-3.7) and 5.6 (95% CI, 3.2-9.8), respectively, when compared with low EBR group. For detecting GD, it was 0.9 (95% CI, 0.5-1.6), 1.0 (95% CI, 0.6-1.6), and 3.8 (95% CI, 1.3-10.6), when compared with low EBR group. EBR values from Unit A and B are presented in **Table 2**.

Overall, for Units A and B combined, the endoscopists' EBR value was strongly correlated with detection of GPC (rho=0.83; *P*<.001) and for GD detection a

trend was seen, however without statistical significance (rho=0.39; *P*=.057) (**Figure 2**).

EBR and missed gastric cancers

For this analysis, we have divided all endoscopists by the EBR median value into higher (≥43.8%) and lower (<43.8%) EBR group to analyze the association between EBR group and the odds of missed cancer during EGD.

A total of 350 GCs were diagnosed at Unit A and B in the study period. This included 288 GCs identified at baseline endoscopy and 62 GCs identified through cross-reference with the National Cancer Registry. Of the latter, 36 GCs were classified as missed cancers (18 in Unit A and 18 in Unit B; median time from EGD to cancer diagnosis: 0.9 years, IQR: 0.4-1.7 years) and 26 as latent cancers (median time from EGD to cancer diagnosis: 7.3 years, IQR: 4.6-8.5 years) (**Figure 1**). The overall GC miss rate was 10.3%. Twenty-nine of the missed cancers were diagnosed among endoscopists with lower EBR (80.6%), and 7 among those with higher EBR (19.4%).

Using a logistic regression model adjusted for patients' age, gender, and endoscopy unit, we have shown that patients examined by endoscopists with higher EBR had a 56% lower risk of missed cancer during EGD as compared with lower EBR group (OR = 0.44; 95% CI, 0.20-1.00; *P*=.049). The incidence of missed GC in the lower EBR group was 49.6 per 100,000 person-years and in the higher EBR group, it was 23.1 per 100,000 person-years. The risk difference was 26.5 per 100,000 person-years (95%CI 1.7-51.4 per 100,000 person-years).

EBR and the rate of negative biopsies

For all endoscopists included in the study we have analyzed the rate of negative biopsies, defined as a proportion of biopsies showing no abnormality in the microscopic assessment among all performed EGDs. This rate varied between endoscopists between 3.5% to 41.0%. The low EBR group had the lowest rate of negative biopsies (mean 10.8%, range 3.5%-20.5%) when compared with other groups because the mean negative biopsy rate for the moderate, high, and very-high EBR groups were 20.5% (range 8.8%-30.0%, *P*=.015), 23.3% (range 5.8%-29.0%, *P*=.007), and 32.2% (range 14.3%-41.0%, *P*<.001), respectively (**Figure 3**).

DISCUSSION

Unlike in the field of colonoscopy, for which multiple quality indicators have been identified (13-15), there are very few performance measures for EGD and most of them are not validated, based on low-quality data, and rarely associated with patient-oriented outcomes. In our study, we have characterized and validated a new performance measure, EBR, basing on a hypothesis that the rate of obtaining biopsies, similarly to polyp detection rate in colonoscopy, broadly reflects the number of abnormalities detected in routine outpatient EGDs. We have found that the biopsy rate was markedly variable between endoscopists, and this was observed both in the derivation cohort (EBR range 22.4%-65.8%) and the external validation cohort (EBR range 22.0%-52.9%). We have shown that the EBR parameter was strongly associated with GPCs detection (rho=0.83; *P*<.001) and, most importantly, with the risk of missed GCs. Decision to use these end-points was supported by a fact that GC is the most common UGI malignancy in Western countries and the GPC detection was previously used in other studies on UGI quality indicators (17). Nevertheless, the utility of EBR was also maintained when we have included all UGI premalignant conditions (GPCs, BE, SIN, DA) in the analysis.

Recently, several gastroenterology societies have published guidelines and statement papers on performance measures for UGI tract endoscopy (5-7). Up to date, the most broadly studied parameter for EGD is the procedure time. For example, an association between the examination time of BE and the detection rate of high-grade dysplasia and adenocarcinoma was shown (16). In a subsequent study by Teh JL et al, (17) endoscopists with mean EGD examination time of more than 7 minutes were more likely to detect precancerous lesions and cancers in the UGI tract, as compared to those with shorter examination time. Finally, a most recent study by Park JM et al (18) found that endoscopists with a mean examination time of more than 3 minutes (withdrawal time after reaching the duodenum and cleaning the gastric mucosa), were more likely to detect gastric adenomas and cancers than "fast endoscopists." In this study, in relation to ours, the frequency of endoscopic biopsies varied significantly among endoscopists (range 6.9%–27.8%) and was strongly correlated with the rate of neoplasm detection (R^2 =0.76; *P*=.015) (18). The biopsy rates were notably lower than those in our study (22.0% - 65.8%); however, the South Korean study involved asymptomatic screening population, whereas our cohort included patients being evaluated for GI symptoms, more often requiring biopsy sampling. To compare, in a previous Japanese study on symptomatic patients, the mean biopsy rate was 55.0%, which was similar to ours; however, the higher rate of GC in Japan and widespread use of advanced imaging techniques is a confounder in this comparison (8).

By cross-linking our data with the National Cancer Registry, we investigated the rate of missed GCs. We identified 36 EGDs negative for cancer, in patients who were diagnosed with GC between 1 month and 3 years afterward. We have used these criteria in accordance with previous studies analyzing the rate of missed upper

GI cancers (4,8-11). The GC miss rate in our cohort was 10.3%. In comparison, a report by Raftopoulos et al (9) has shown a missed cancer rate of 6.7% in a cohort of 28,000 patients. This number, however, included all UGI cancers (duodenum, stomach, and esophagus). When including only GCs, the missed cancer rate was 4.3%, which is over 2-fold lower than in our study. On the other hand, previous Asian studies reported a missed GC rate of 14% and 26% (8,10), which is substantially higher than it was shown in our study. These reports, however, originate from countries with a high incidence of GCs, with different histological criteria for cancer.

The EBR parameter was assessed using a large dataset of nearly 30,000 EGDs performed by 26 endoscopists. The main strength of our study is that it includes an external validation in a high-volume, geographically distinct unit. EBR parameter is easy to calculate because it only requires the number of EGDs with at least one biopsy obtained from any part of the UGI tract (this can be determined by ICD-9 coding) and the total number of procedures. In the EBR calculations we included EGDs with biopsies obtained from any part of the UGI tract (esophagus, stomach, duodenum) to make the EBR calculation as simple as possible. We have shown that EBR is associated with the detection of all UGI premalignant conditions, however in presenting our results we have focused on gastric findings (GPC detection and rate of missed GCs) as a surrogate end-point to objectively compare endoscopists' performance, as was done in previous studies (17).

Our study was limited by a few relevant factors, and a retrospective design is the main one. It needs to be emphasized that the EBR parameter was developed in the setting of routine outpatient endoscopy units and is not applicable in inpatient setting, where therapeutic procedures constitute a significant proportion of examinations. Unit A and B differed significantly in terms of GPC detection, and this

can be explained by difference in expertise because Unit A is a endoscopy unit based around oncology center and Unit B is based around general gastroenterology department. Despite those differences in performance, we could still show a meaningful difference in performance between EBR group's in the validation cohort, which proves the reproducibility of this parameter. It must be underlined, that our electronic database did not include information on patients' risk factors, such as smoking, medications, body mass index and the use of advanced imaging techniques, such as virtual chromoendoscopy. Most of the procedures were performed using standard video-resolution endoscopes, which represents the standard of care in routine outpatients' endoscopy practice within the time frames of the study. This, on one hand, has the advantage of uniform (hence comparable) equipment being used among endoscopists in our study, but on the other hand, it does not represent the current shift in standard of care toward high-definition endoscopy. Moreover, we did not have the procedure time recorded in our databases. This limitation is important because we believe that EBR and procedural time might be correlated with each other and both of these parameters represent the quality of mucosal inspection during EGD. Lastly, we could not extract the data on the distribution and extension of the GPCs. This limitation is particularly important in terms of atrophic gastritis, which is associated with significant risk of cancerous change when diffused or multifocal, however low risk (not requiring surveillance) when only limited to the gastric antrum (19). We also did not have data on whether biopsy protocols, such as the Sydney protocol (20), were followed in both units and could not differentiate whether biopsies were targeted or random. We are also aware, that just like polyp detection rate in colonoscopy, EBR parameter might be susceptible for "gaming." (21) One could believe, that knowing about the EBR

parameter being monitored may encourage endoscopists to take more random biopsies to boost their EBR value without influencing the patients' outcome. A potential solution to this problem could be adjusting the EBR parameter to the rate of GPCs diagnosis for each endoscopist.

The utility of EBR requires further evaluation in prospective trials to determine the most accurate range of its value, that would represent the highest diagnostic yield, and the lowest cost burden at the same time. Increasing EBR values are associated with growing number of negative biopsies, hence costs, and our study may suggest that endoscopists within high EBR group (43.8%-51.6%) represent the best balance between UGI high-risk lesion detection and missed GC diagnoses and the rate of negative biopsies (costs).

We are aware, however, that the EBR parameter is dependent on the regional prevalence of the GPC and GC. Therefore, rather as an absolute value, EBR should be used to compare endoscopists within the same unit/region, to see the variation of its value, and to identify endoscopists requiring improvement. In our view, EBR is a parameter which indirectly informs about the quality of inspection of gastric mucosa (like procedure time). Meticulous inspection of the mucosa translates into better endoscopic recognition of GPCs, which needs to be confirmed with a biopsy. The higher rate of GPCs diagnoses is also of value for the patients, who are then triaged to the population of increased GC risk in the future.

In conclusion, endoscopists' biopsy rate (EBR) is highly variable, and we believe that within a group of comparably experienced endoscopists it correlates with a detection rate of mucosal abnormalities in the upper GI tract during EGD. This is the first study to describe and analyze EBR as a quality indicator for routine

diagnostic outpatient EGD and to show its correlation with important, patient-oriented outcomes such as GPC detection and the rate of missed GCs.

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Table 1. Derivation cohort (Unit A) characteristics

	EGDs (%)	All GPC*	Atrophic gastritis	Intestinal metaplasia	Gastric Dysplasia	Gastric Cancer
All patients	15,340 (100%)	1,331 (8.7%)	318 (2.1%)	825 (5.4%)	188 (1.2%)	188 (1.2%)
Age groups (median age = 57 years, range: 18 - 91)						
18 - 49	4,371 (28.5%)	174 (1.1%)	53 (0.3%)	100 (0.7%)	21 (0.1%)	25 (0.2%)
50 - 69	7,992 (52.0%)	727 (4.7%)	168 (1.1%)	459 (3.0%)	100 (0.6%)	106 (0.7%)
≥ 70	2,997 (19.5%)	430 (2.8%)	97 (0.6%)	266 (1.7%)	67 (0.4%)	57 (0.3%)
Gender						
Female	8,976 (58.5%)	728 (4.7%)	197 (1.3%)	452 (2.9%)	79 (0.5%)	63 (0.4%)
Male	6,364 (41.5%)	603 (3.9%)	121 (0.8%)	373 (2.4%)	109 (0.7%)	125 (0.8%)
Indications						
Benign symptoms **	7,766 (50.6%)	516 (3.3%)	147 (0.9%)	321 (2.1%)	48 (0.3%)	21 (0.1%)
Alarm symptoms ***	1,691 (11.0%)	190 (1.2%)	67 (0.4%)	109 (0.7%)	14 (0.1%)	28 (0.2%)
Others	5,883 (38.4%)	625 (4.1%)	104 (0.7%)	395 (2.6%)	126 (0.8%)	139 (0.9%)

*- atrophic gastritis, intestinal metaplasia and gastric dysplasia

**- dyspepsia, abdominal pain, reflux,

***- anaemia, GI bleeding, dysphagia, weight loss, emesis;

EBR- endoscopists' biopsy rate; EGD- esophagogastroduodenoscopy; GPC- gastric precancerous conditions

Table 2. Endoscopists and EBR group characteristics for Derivation and Validation cohorts (Unit A and Unit B)

Endo-scopist	EBR	EGDs	GPC (%)*	GD (%)	EBR Group (EBR range)	OR for GPC	95% CI	OR for GD	95% CI
Derivation cohort (EGD n=15,340)									
1	22.4	1,700	41 (2.4%)	6 (0.3%)	Low EBR (22.4-36.7%)	1.0	-	1.0	-
2	23.4	470	25 (5.3%)	2 (0.4%)					
3	28.4	264	10 (3.8%)	1 (0.4%)					
4	35.5	2,738	197 (7.2%)	29 (0.5%)					
5	37.9	140	8 (5.7%)	0 (0.0%)	Moderate EBR (36.8-43.7%)	1.6	1.3-1.9	2.1	1.1-3.9
6	40.5	1,714	131 (7.6%)	24 (0.6%)					
7	40.9	428	44 (10.3%)	14 (1.2%)					
8	43.2	273	20 (7.3%)	4 (1.1%)					
9	44.1	290	24 (8.3%)	3 (0.7%)	High EBR (43.8-51.6%)	2.0	1.7-2.4	2.7	1.5-4.7
10	46.1	1,682	139 (8.3%)	24 (0.6%)					
11	49.1	422	49 (11.6%)	9 (1.4%)					
12	50.2	1,272	156 (12.3%)	23 (1.4%)					
13	53.0	415	51 (12.3%)	4 (0.5%)	Very-High EBR (51.7 - 65.8%)	2.5	2.1-2.9	1.9	1.1-3.4
14	55.3	517	57 (11.0%)	4 (0.4%)					
15	58.6	278	30 (10.8%)	2 (0.7%)					
16	65.8	2,737	349 (12.8%)	39 (0.8%)					
Validation cohort (EGD n=14,294)									
A	22.0	413	0 (0.0%)	0 (0.0%)	Low EBR	1.0	-	1.0	-

B	22.4	339	3 (0.9%)	3 (0.9%)	(22.0 - 36.7%)				
C	27.4	3,289	52 (1.6%)	17 (0.5%)					
D	30.4	1,656	47 (2.8%)	26 (1.6%)					
E	30.5	617	16 (2.6%)	4 (0.6%)					
F	35.4	3,689	82 (2.2%)	31 (0.8%)					
G	41.2	1,338	21 (1.6%)	9 (0.7%)	Moderate EBR (36.8–43.7%)	0.8	0.5–1.2	0.9	0.5–1.6
H	42.1	447	6 (1.3%)	3 (0.7%)					
I	47.1	2,387	43 (1.8%)	21 (0.9%)	High EBR (43.8–51.6%)	3.0	2.4–3.7	1.0	0.6–1.6
J	52.9	119	15 (12.6%)	4 (3.4%)	Very-High EBR (≥51.7%)	5.6	3.2-9.8	3.8	1.3-10.6

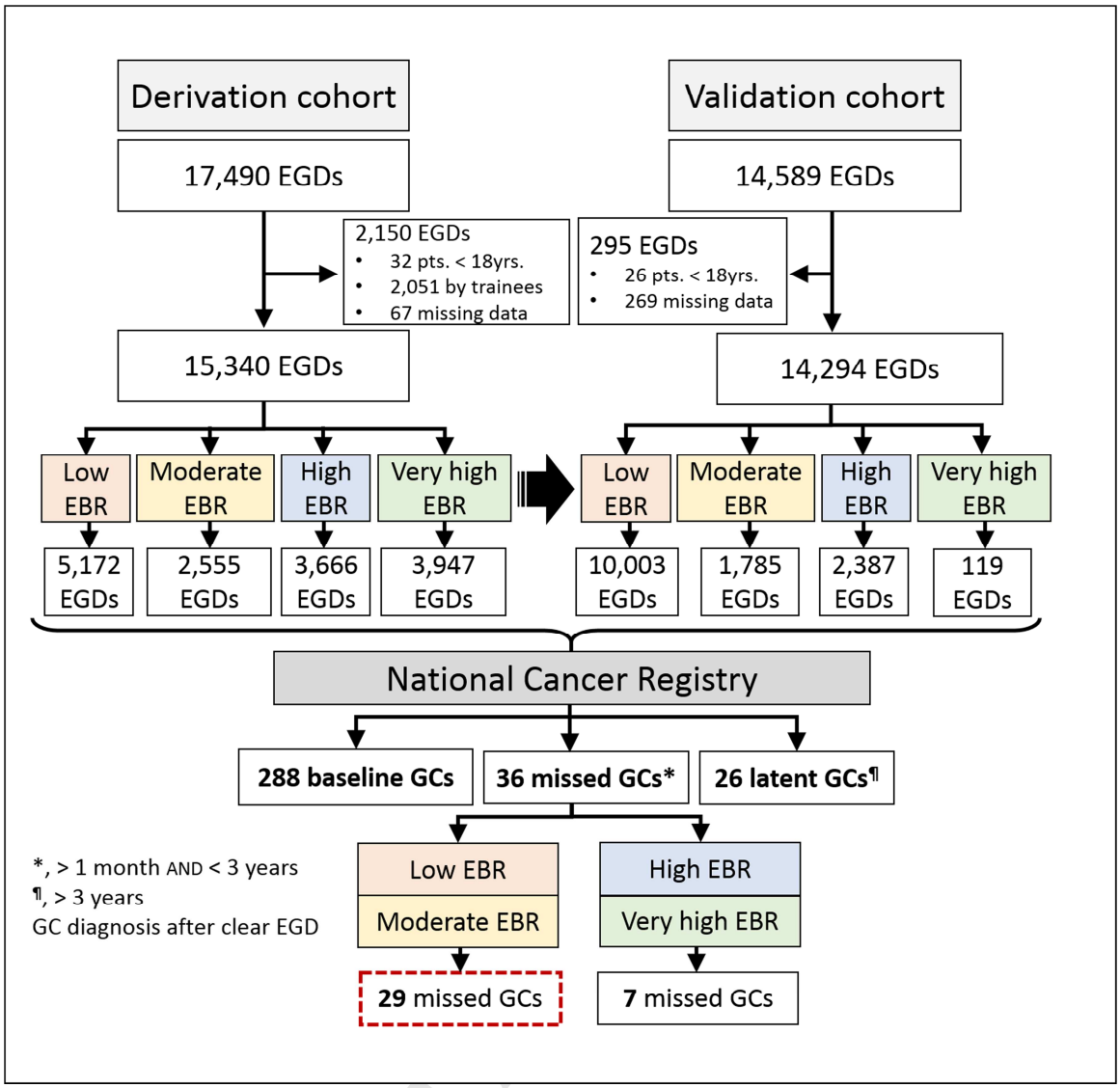
*- including atrophic gastritis, intestinal metaplasia, low-, indefinite-, and high- grade dysplasia

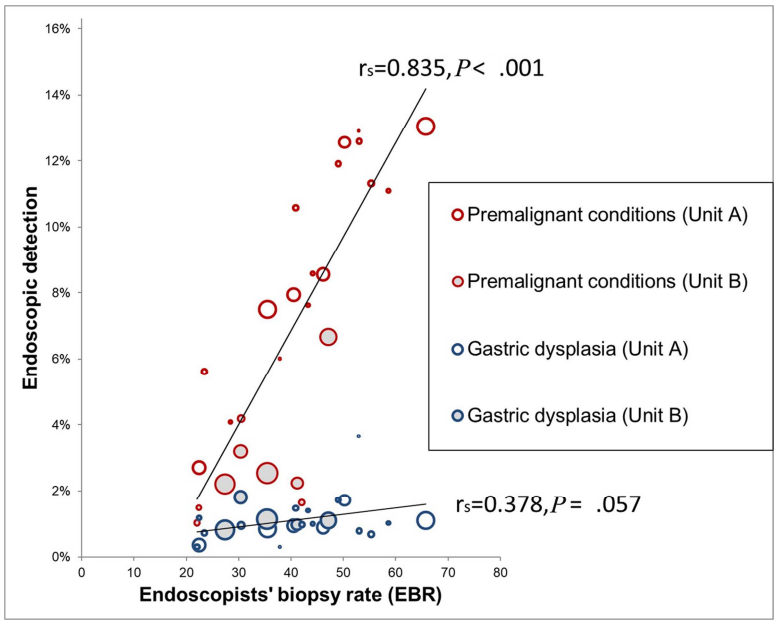
EBR, endoscopists biopsy rate; EGD, esophagogastroduodenoscopy; GD, gastric dysplasia; GPC, gastric precancerous conditions; OR, Odd Ratio

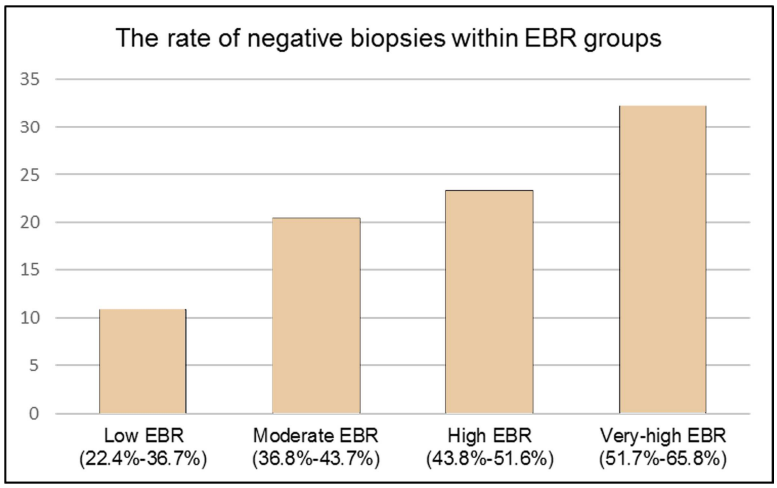
Figure 1. Study flowchart. EGD, Esophagogastroduodenoscopy; EBR, endoscopists biopsy rate; GC, gastric cancer.

Figure 2. Combined data from Unit A and Unit B showing association between endoscopists' biopsy rate and detection of gastric premalignant conditions *(red circles)* and dysplasia *(blue circles)*. Each circle represents single endoscopists' performance and the diameter of the circle corresponds to the number of endoscopies performed by endoscopist. r_s- Spearman correlation.

Figure 3. The rate of negative biopsies within the EBR groups. EBR, Endoscopists' biopsy rate.







Abbreviations

BE – Barrett's esophagus

DA – Duodenal adenoma

EGD - Esophagogastroduodenoscopy

EBR – Endoscopists' biopsy rate

GC – Gastric cancer

GD – Gastric dysplasia

GPC – Gastric precancerous condition

OR – Odds Ratio

SIN – Squamous intraepithelial neoplasm

UGI – Upper gastrointestinal tract