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Title

Red dichromatic imaging and linked color imaging as reliable image-enhanced endoscopic procedures for detecting the distal end of the palisade vessels in the columnar metaplastic mucosa of the gastroesophageal junction zone

Short title

RDI and LCI for DEPV in GOJZ

Authors

Satoshi Ono Dr., Ph.D.1)8), Keiko Yamamoto Dr., Ph.D.2), Fumiaki Ishibashi Dr., Ph.D.3), Ai Fujimoto Dr., Ph.D.4), Yuji Urabe Dr., Ph.D.5), Tsutomu Takeda Dr., Ph.D.6), Hideki, Ishikawa Dr., Ph.D.7), Mitsuhiro Fujishiro Dr., Ph.D.8), Takuji Gotoda Dr., Ph.D.9), Michio Kaminishi Dr., Ph.D.10), Kentaro Sugano Dr., Ph.D.11)

Affiliations

- 1) Department of Gastroenterology and Gastrointestinal Endoscopy, Tokyo Metropolitan Institute for Geriatrics and Gerontology, Tokyo, Japan
- 2) Division of Endoscopy, Hokkaido University Hospital, Sapporo, Japan

Department of Gastroenterology and Hepatology, Graduate School of Medicine, Hokkaido University, Sapporo, Japan

3) Department of Gastroenterology, International University of Health and Welfare Ichikawa Hospital, Chiba, Japan

4) Department of Gastroenterology and Hepatology, Division of Internal medicine, Toho University Omori Medical Center, Tokyo, Japan

5) Department of Gastroenterology, Hiroshima University Hospital, Hiroshima, Japan.

6) Department of Gastroenterology, Juntendo University School of Medicine, Tokyo, Japan.

7) Department of Molecular-Targeting Prevention, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

8) Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

9) Department of Gastroenterology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

10) Department of Gastroenterology, Tamaryokuseikai Foundation, Tokyo, Japan

11) Department of Internal Medicine, Division of Gastroenterology, Jichi Medical University, Tochigi, Japan

Correspondence

Keiko Yamamoto, MD, Ph.D.

Division of Endoscopy, Hokkaido University Hospital, Kita 14 Nishi 5, Kita-Ku, Sapporo,

060-8648, Japan

Department of Gastroenterology and Hepatology, Graduate School of Medicine, Hokkaido

University, Sapporo, Japan

keiko_sannai@yahoo.co.jp

ABBREVIATIONS AND ACRONYMS

CMM: columnar metaplastic mucosa

GEJ: gastroesophageal junction

RE: reflux esophagitis

DEPV: distal end of palisade vessel

PEGF: proximal end of gastric fold

IEE: image-enhanced endoscopy

NBI: narrow-band imaging

BLI: blue-laser imaging

RDI: red dichromatic imaging

LDI: linked color imaging

TXI: texture imaging

JGES: Japan gastroenterological endoscopy society

O-WLI: Olympus white-light imaging

F-WLI: Fujifilm white-light imaging

RSL: radial straight line

CV: coefficient of variance

Author contributions

SO, FI, KY, AF, YU, and TT equally contributed to study conception and design, interpretation of data, and preparation of the manuscript. SO contributed to the collection of data and drafting of the manuscript. FI contributed to the statistical analysis of the data. HI, MF, TG, MK, and KS contributed to the critical review of the study design and final approval of the article.

Key words

Gastroesophageal junction; endoscopy; mucous membrane

Abstract

Background and study aims: There is a consensus that identifying the distal end of the palisade vessels (DEPV) is important for diagnosing gastroesophageal junction (GEJ). However, optimum observation methods have not been established. This study investigated the use of effective image-enhanced endoscopy (IEE) for DEPV detection.

Methods: One hundred endoscopic images in 20 cases of columnar metaplastic mucosa of the GEJ recorded with white-light imaging (Olympus-WLI and Fujifilm-WLI) and IEEs (narrow-band imaging; RDI1/2/3, red dichromatic imaging; texture and color enhancement imaging 1/2; blue-laser imaging; and LCI, linked color imaging) from two manufacturers were extracted and evaluated by 10 evaluators. Up to 24 radial straight lines from the center of the lumen were placed on the image, and the evaluators placed markings according to confidence level (high, low, and not detectable) at the DEPV locations. The detectability and reproducibility at the rate of the confidence level and coefficient of variance of markings among the evaluator were analyzed.

Results: In total, 15,180 markings were obtained. In terms of detectability, RDI1 (49.4%), RDI2 (53.0%), RDI3 (54.1%), TXI2 (49.7%), and LCI (34.6%) had a significantly higher rate of high confidence among the IEEs in each manufacturer. By contrast, Olympus-WLI (40.6%), Fujifilm-WLI (17.6%), narrow-band imaging (15.9%), and blue laser imaging

(9.8%) presented with a significantly lower rates of high confidence. Regarding reproducibility, RDI3 and LCI had the lowest coefficient of variance for each manufacturer.

Conclusions: RDI and LCI could be reliable modalities for detecting DEPVs in the columnar metaplastic mucosa of the GEJ zone.

Introduction

Esophageal adenocarcinoma, which is the major histopathologic type of esophageal cancer in Western countries, mainly originates from the columnar dysplastic mucosa (CMM) of the esophagus.¹⁻³ The diagnosis and regular follow-up of CMM, in which the squamous epithelium of the esophagus is replaced by columnar epithelium due to reflux esophagitis (RE), are important for the early detection and treatment of adenocarcinoma.⁴ Therefore, the gastroesophageal junction (GEJ) is an important landmark in defining conditions that occur in this region, which include the presence and length of the CMM, cancer localization in the GEJ, and its site of origin.

However, the diagnosis of CMM in the GEJ, either at the distal end of the palisade vessel (DEPV) or the proximal end of the gastric fold (PEGF), has long been controversial.⁵⁻⁷ This is because the visibility of the DEPV is compromised by inflammation caused by RE. Meanwhile, the visibility of the PEGF is compromised by severe atrophy attributed to *Helicobacter pylori* infection.⁸ Therefore, the GEJ is commonly diagnosed at the PEGF among patients in Western countries, where RE is more common, and at the DEPV among patients in Asian countries, where the *Helicobacter pylori* infection rate is high.

Hence, an international meeting was convened in Kyoto to compare the variation in the endoscopic diagnosis of GEJ using the Japanese and Prague C&M criteria as a landmark of

the GEJ. Then, an international consensus was developed.⁹⁻¹¹ In this international consensus, the identification of the anatomic DEPV beneath the CMM layer is considered more important in diagnosis at the GEJ than that at the PEGF.¹² However, the preferred method of endoscopic observation for DEPVs has not yet been established.

For some time, image-enhanced endoscopy (IEE), which improves the visibility of major blood vessels in the shallow layers, particularly in narrow-band imaging (NBI) and blue-laser imaging (BLI), has greatly contributed to the diagnosis of early-stage cancer in the gastrointestinal tract.¹³⁻¹⁶ In addition, recently developed red dichromatic imaging (RDI) has improved the visualization of blood vessels in deeper layers based on different principles.¹⁷⁻²⁰ Furthermore, in addition to linked color imaging (LCI), which is characterized by color enhancement technology, texture and color enhancement imaging (TXI), which combines color, texture, and brightness enhancement, has been newly developed.^{21,22} Some studies have also reported about the usefulness of LCI or TXI in CMM.²³⁻²⁶ These IEEs may be useful for identifying DEPV. However, no study has evaluated the usefulness of various IEEs for identifying DEPV in the GEJ zone.

Therefore, this study aimed to determine effective IEE for DEPV diagnosis by objectively evaluating endoscopic images of the GEJ zone obtained using different IEEs.

Materials and methods

Study design

This multicenter study was approved by the Ethics Committee of the Tokyo Metropolitan Institute for Geriatrics and Gerontology. Further, five institutions were authorized to conduct the study. The flowchart in Figure 1 shows the study design. In this study, the endoscopic images recorded with various IEEs of the GEJ zone, which were prepared in advance and arranged randomly, were evaluated by third-party endoscopists. Data on detectability, which is the primary endpoint, and reproducibility, which is the secondary endpoint, were aggregated according to the following method.

Study participants

In total, 10 evaluators one beginner and one nonbeginner from each of the five institutions agreed to participate in the study. Beginners were defined as trainees without Japan Gastroenterological Endoscopy Society (JGES) certifications of fellow that require an experience of 1000 upper gastrointestinal endoscopy and/or 200 lower gastrointestinal endoscopic procedures. Nonbeginners were defined as trainers with the JGES certifications of trainer.²⁷ All of the evaluators have experience with endoscopes from the two manufacturers described below. In daily clinical practice, six of the ten evaluators use systems from both

manufacturers equally, while the remaining four mainly use systems from one manufacturer.

Data collection

All endoscopic images were recorded with endoscopic systems from Olympus (GIF-H290Z, GIF-H290T, GIF-XZ 1200, or GIF EZ1500 as scopes with EVIS X1 CV-1500 as processors; Olympus Corp., Tokyo, Japan) or Fujifilm (EG-L580NW7, EG-L580NW, EG-L590WR, EG-L590ZW, EG-L600WR7, EG-L600ZW7, or EG-L600ZW as scopes with LASERIO VP-7000, LASERIO VP-4450HD as processors; Fujifilm Holdings Corp., Tokyo, Japan). The images involving the GEJ zone recorded with Olympus white-light imaging (O-WLI) and six IEE modes (NBI, RDI1, RDI2, RDI3, TXI1, and TXI2) and the images involving the GEJ zone recorded with Fujifilm white-light imaging (F-WLI) and two IEE modes (BLI, LCI) were collected from consecutive cases in five institutions between December 2022 and February 2023. In order to evaluate the effect of IEE in isolation, no magnification function of the endoscope was used for imaging in this study. All images were reviewed by five experts of the study team (YK, OS, FA, YU, and TT) to exclude images inappropriate for this evaluation due to poor imaging conditions. Cases in which images could not be evaluated due to darkness, light artifacts, or contamination, as well as cases in which DEPV could not be confirmed in any mode, were excluded. To properly conduct this study, the images of 10 Olympus cases

and 10 Fujifilm cases were selected using the preliminary score of five experts (Figure 1). In each selected 10 cases, all images with all modes were recorded in the same composition. Of the 10 cases, 5 were imaged in close-up view with a part of the GEJ zone captured. The other five cases were imaged in distant view with the full circumference of the GEJ zone captured.

The details of all IEEs in Figure 1 are shown below:

NBI: IEE to enhance the visibility of the superficial blood vessels, comprising blue (415 nm) and green (540 nm) wavelengths.¹³⁻¹⁵

RDI: IEE to enhance the visibility of the deep blood vessels, comprising green (540 nm), amber (600 nm), and red (630 nm) wavelengths. Modes 1, 2, and 3 are designed to identify bleeding points during endoscopic treatment, enhance the deeper vessels for better detection via the mucosal layer, and enhance mucosal tissues beyond the overlying mucus residue, respectively.¹⁷⁻²⁰

TXI: IEE to enhance differences in the color, texture, and brightness of the mucosal surface.

Modes 1 and 2 are designed to emphasize differences in color and texture, respectively.^{22, 25}

BLI: IEE to enhance the visibility of superficial blood vessels, comprising two blue-wavelength laser beams (410 and 450 nm).¹⁶

LCI: IEE to enhance the color contrast after image processing, comprising two blue-wavelength laser beams (410 and 450 nm). The balance of the two laser light intensities differs

from BLI.^{21, 23, 24}

Only one of the 20 Fujifilm had a long segmental CMM. Two of the 20 Olympus cases and four of the 20 Fujifilm cases had mild RE, such as grade M or A in the Los Angeles classification. In order to evaluate the effect of IEE in isolation, no magnification function of the endoscope was used for imaging in this study.

The captured IEE images were processed for evaluating DEPV. The center point of the radial straight lines (RSLs) was set at the point where the direction of the DEPVs meets. In total, 24 radiation lines were placed every 15° from the center point. A test form for evaluating DEPV was created for each endoscopic image that was embedded in the presentation files of the PowerPoint software (Microsoft Corp., Redmond, the USA). In this step, several images were rotated and fine-tuned as required. Hence, the RSLs matched between each image of the same case. If the DEPV was not visible because of lens contamination, darkness, or being out of the field of view, the corresponding RSL was excluded from evaluation in all IEE images of the same case. All images were arranged randomly before evaluation (Figure 2).

Evaluation of the DEPV

The types of marks (circular or triangle symbol) and the distance of the marks from the center point of the radiation were aggregated for detectability and reproducibility, respectively

(Figure 3). These data were extracted using the ImageJ software (National Institutes of Health, Bethesda, Maryland, the USA).²⁸ The standardized distance was calculated by dividing each distance by the average distance between 10 evaluators on the same image in the same IEE on the RSL in the same direction. This standardized distance represents the value relative to the average value of the distances. To analyze the standardized distance, RSLs where DEPVs were detected by none or only one evaluator were excluded from the analysis because they were inappropriate for the analysis of variance of the standardized distance defined above. To analyze reproducibility, the coefficient of variance (CV) for each endoscopic image was calculated based on the variance of standardized distance among evaluators.

Statistical analyses

All statistical analyses were performed using the R software (R Core Team, Vienna, Austria).²⁹ To analyze detectability, the significance difference test was performed to evaluate the difference in the percentage of high-confidence within each IEE. In this analysis, the relative superiority and inferiority of the individual IEEs in comparison to the overall trend were evaluated. No comparisons were made among the individual IEEs. The methods used were the chi-square test, residual analysis for in-group comparison, and multiple comparison correction using the Bonferroni method. The average CV for each IEE was compared using

the Student's t-test with multiple comparison correction using the Bonferroni method. P-values of 0.05 were considered significant.

This study was registered in the UMIN clinical trial registry (UMIN000053048).

Results

The data of 15,180 RSLs were obtained from the evaluated images.

Detectability

Figure 4 and Supplementary Table 1 show the overall summary of the confidence levels for detecting DEPV on all RSLs. Among the IEEs of the Olympus system, RDI1, RDI2, RDI3, and TXI2 had a significantly higher ratio of high confidence for detection. In contrast, O-WLI and NBI presented with a significantly lower ratio of high confidence for detection. Among the IEEs of the Fujifilm System, LCI had a significantly higher ratio of high confidence for detecting DEPVs. F-WLI and BLI had a significantly lower ratio of high confidence.

Figure 5 and Supplementary Table 2 present the confidence levels for detecting DEPVs by comparing distant and close-up images. Based on the statistical analysis of each image group, RDI3, TXI2, and LCI had a significantly higher ratio of high confidence for detecting DEPVs

in both distant and close-up view images. In contrast, O-WLI had a significantly higher ratio of high confidence in distant view images.

Figure 6 and Supplementary Table 3 show the confidence levels for detecting DEPVs between beginners and nonbeginners. Both beginners and nonbeginners presented with significantly higher high confidence rates for RDI2, RDI3, TXI2, and LCI. However, there was a divergence. That is, beginners also had a higher high confidence rate in O-WLI. Meanwhile, nonbeginners had a lower high confidence rate in O-WLI.

Reproducibility

Figure 7 shows the CV of the standardized distance for each IEE. A smaller CV of the standardized distance indicates a higher reproducibility between evaluators. Based on this viewpoint, the RDI3 and LCI are IEEs with the highest reproducibility in the Olympus and Fujifilm systems, respectively.

Discussion

Considering the consensus developed in the Kyoto International Meeting, there was an urgent need to establish optimal conditions for the endoscopic detection of DEPVs in daily clinical

practice. In this context, the current study revealed the optimal IEEs for detecting DEPVs with high detectability and reproducibility. Based on our results on detectability, RDI3, TXI2, and LCI could be reliable IEEs for detecting DEPVs in the GEJ zone, particularly in close-up observation. In addition, RDI3 and LCI could reduce the variability between endoscopists based on the reproducibility results. Considering that the current research showed that O-WLI could be reliable in distant observation, DEPVs should be detected via close-up observation with RDI3 in cases where the CMM in the GEJ zone is suspected via distant observation using O-WLI in institutions where the Olympus system is available. Furthermore, for endoscopists who have only observed the esophagus with WLI, NBI, or BLI, the use of RDI or LCI when observing the GEJ may improve the visibility of the DEPV and make it available as a landmark in the GEJ.

Due to the design of this study, the cases prepared for evaluating IEEs from the two manufacturers differed. Therefore, these IEEs between the two manufacturers cannot be compared. However, it could identify IEEs with high detectability and reproducibility for GEJ diagnosis in the IEEs of each manufacturer. Even though there may be bias caused by the system used mainly by each institution to which the evaluators belong, each of these IEEs was identified to help detect DEPVs in each system. In fact, based on the environment of the endoscopy system in each institution, observation with F-WLI may be acceptable if combined

with LCI in close-up observation.

One of the reasons for the improved visibility of DEPV in RDI and LCI can be attributed to the component wavelength, which can reach deeper layers of the mucosa.¹⁷⁻²² Anatomically, DEPV is a blood vessel that runs in the deeper layer of the proper lamina.³⁰ In RDI, DEPV can be effectively delineated by originally selecting light with a longer wavelength to delineate deep blood vessels. Regarding the other IEEs, including TXI and LCI, the enhancement of color and texture without loss of depth information may improve the visibility of DEPV. However, IEEs, such as NBI and BLI, which specialize in the delineation of shallow vessels, can reduce the visibility of DEPV because of the loss of information on deep vessels, including the DEPV. The results of this study support this notion. It is not clear why RDI3 was more effective than RDI1 and RDI2, which have similar mechanisms. If anything, it is speculated that the color contrast of RDI3 may have been influenced by a greater emphasis on the visibility of blood vessels.

Further, this study revealed that RDI, TXI, and LCI were effective for DEPV detection regardless of the endoscopist's proficiency level. Thus, even inexperienced endoscopists or endoscopists in countries where endoscopy is not widely used may find it easier to recognize DPEVs using such IEEs. The reason why nonbeginners had a lower high confidence rate in O-WLI is not clear. However, we hypothesized that nonbeginners are more cautious than

beginners regarding DEPV identification under WLI. In relation to this, beginners and non-beginners may recognize different vessels as palisade vessels. However, such IEEs are effective in bridging the gap between beginners and nonbeginners. Undeniably, an endoscopist must gain experience for overall DEPV identification. Several studies have shown that e-learning is effective in the field of endoscopy.^{31, 32} Hence, a system must be established to train beginners via education with e-learning using images of the GEJ zone.

The impact of RE on DEPV identification using IEE should also be considered. In clinical practice, cases of CMM in the GEJ zone affected by RE are often encountered. Thus, the PEGF is often used as an alternative to the DEPV in Western countries because of the reduced visibility of the DEPV caused by inflammation of RE, as mentioned in the previous text.⁶ Therefore, the influence of RE on DEPV detection should also be investigated. However, this study only used images of cases in which the DEPV could be identified by either IEE. Therefore, the effect of esophagitis on IEE, which was considered suitable for detecting DEPVs, must be examined in the upcoming study. In addition, the effect of acid secretion inhibitors in such cases should be examined in another study.

This study had several limitations. First, the number of cases and evaluators was small. Second, biases caused by the system that the evaluator mainly uses in daily clinical practice, as mentioned in the previous text, might have existed. Third, because of the statistical analysis

method used in this study, the trend of superiority or inferiority of each IEE was assessed even though it was not designed to compare diagnostic efficacy among the IEEs. Therefore, a multicenter prospective study must be performed to evaluate the actual clinical efficacy of each IEE. Fourth, the image quality degradation caused by embedding images in PowerPoint files might have also affected the study results. However, this step unifies the resolution of all images, which could have made it possible to evaluate differences with IEEs alone, independent of the resolution of the system or scope. It is also important to consider the potential limitations of subjective image evaluation, including high-confidence and low-confidence ratings. Finally, whether the endoscopically visible vessels in this study were truly anatomic DEPVs was not examined. Indeed, pathological studies on the palisade vessels are planned by a subgroup of the GOJZ consortium. However, this study showed the usefulness of endoscopically identifying landmarks for diagnosing CMM. Although a pathological assessment of CMM was not conducted in this study, the results are clinically significant in this context.

In conclusion, RDI and LCI could be reliable modalities for detecting the DEPVs in CMM in the GEJ zone. In cases where the presence of CMM was suspected, close-up and cautious observation should be performed using these IEEs. Furthermore, in the future, a prospective clinical study must be conducted to validate our findings.

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Figure legends

Figure 1. Example of images of the CMM of the GEJ zone in WLIs and IEEs.

Figure 2. Flowchart of this study.

Figure 3. Example of the post-evaluation images of DEPVs.

a. Image of the WLI in distant view.

b. Image of RDI1 in distant view.

c. Image of WLI in close-up view.

d. Image of RDI1 in close-up view.

Figure 4. Summary of the confidence levels for detecting DEPV on all RSLs.

*: significantly inferior ($P < 0.05$), **: significantly superior ($P < 0.05$)

Figure 5. Subanalysis of the confidence levels for detecting DEPV with consideration of distant and close-up views.

*: significantly inferior ($P < 0.05$), **: significantly superior ($P < 0.05$)

Figure 6. Subanalysis of the confidence levels for detecting DEPV between beginners and nonbeginners.

*: significantly inferior ($P < 0.05$), **: significantly superior ($P < 0.05$)

Figure 7. Coefficient of variance of standardized distance for each IEE.

Supplementary Table1. Specific values of the confidence levels for detecting DEPV on all

RSLs.

Supplementary Table2. Specific values of the confidence levels for detecting DEPV with consideration of distant and close-up views.

Supplementary Table3. Specific values of the confidence levels for detecting DEPV between beginners and nonbeginners.

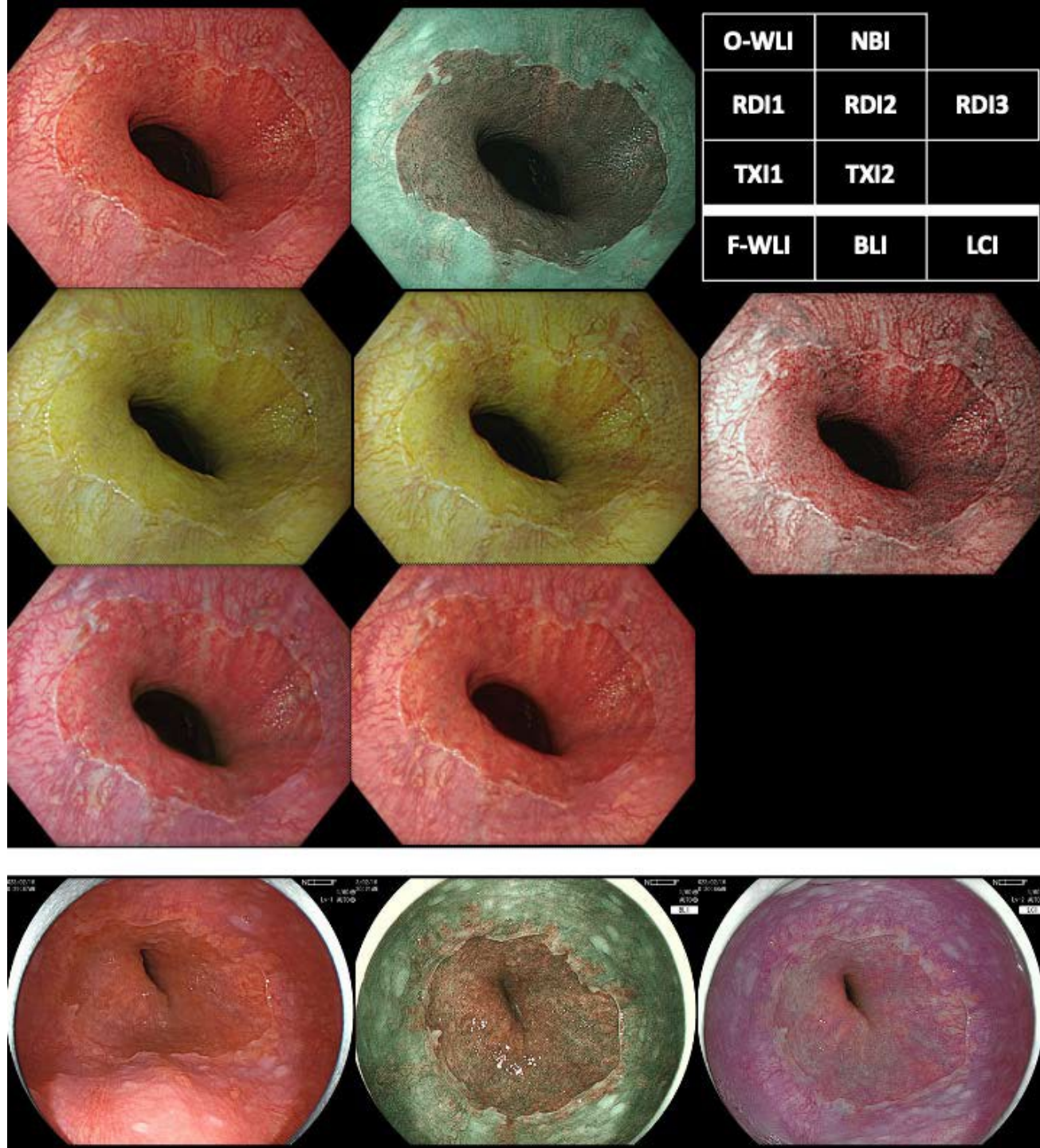
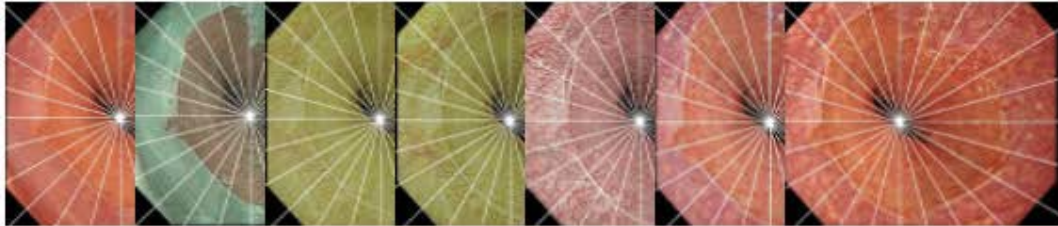


Figure 1

Prepare the 100 images of 20 CMM cases of WLI and IEEs.

Place RSLs at 15 degrees intervals in all images.



Ten endoscopists evaluate the 100 images and place markings at the DEPV on all RSLs according to levels of confidence.



Aggregate the data of the kinds and the distance from the center of the all markings in the images.



Statistical analysis of data of a total of 15,180 markings.

Figure 2

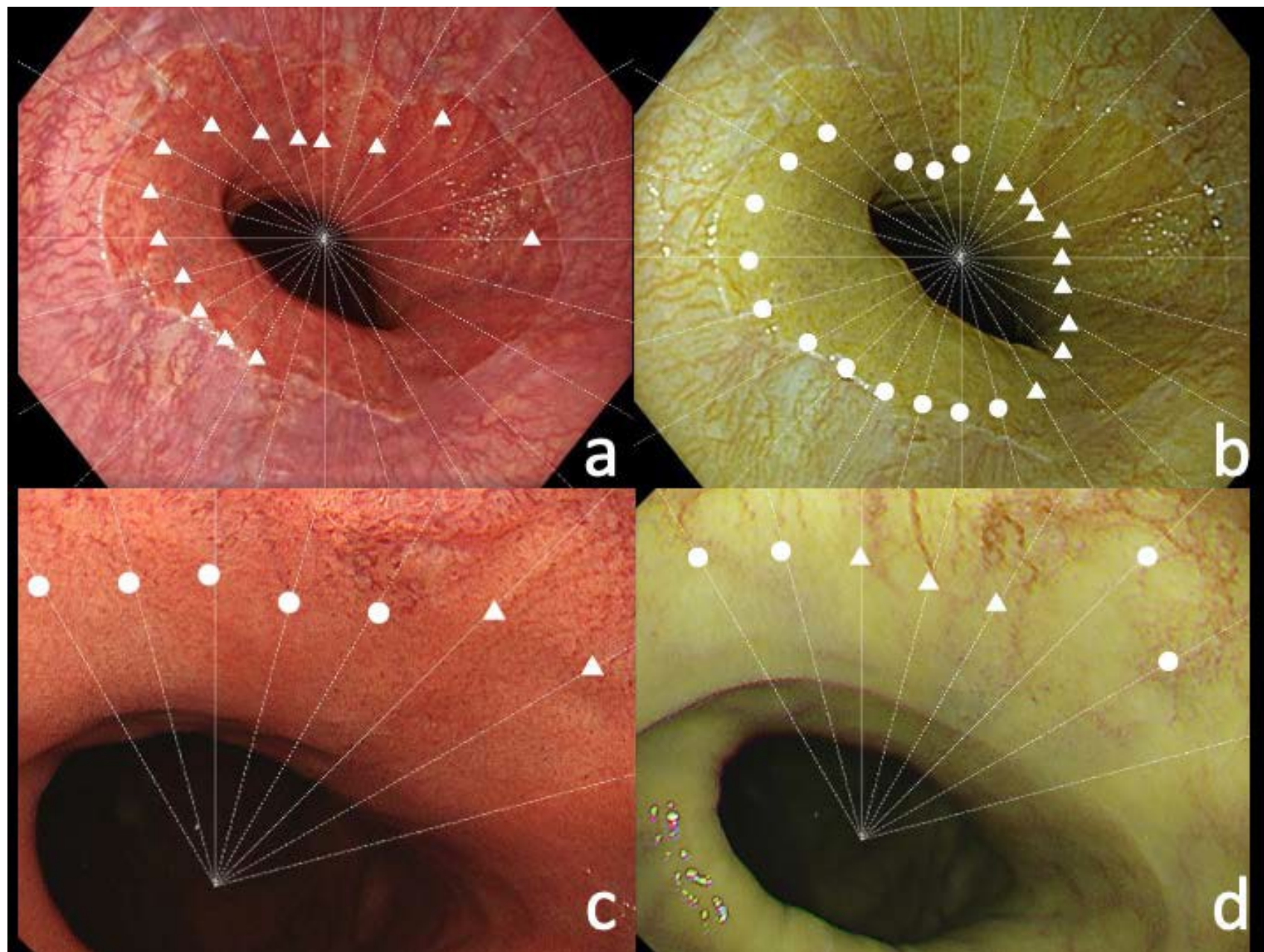


Figure 3

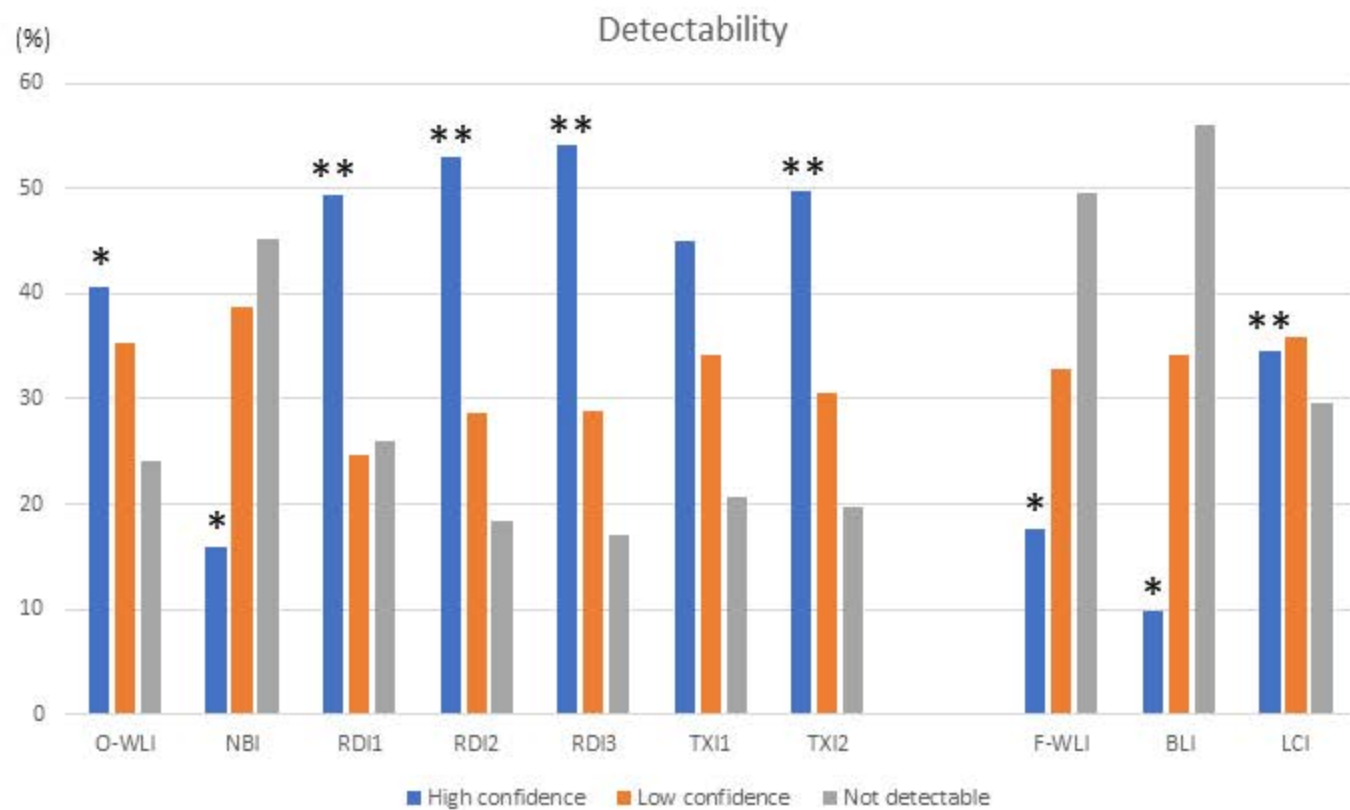


Figure 4

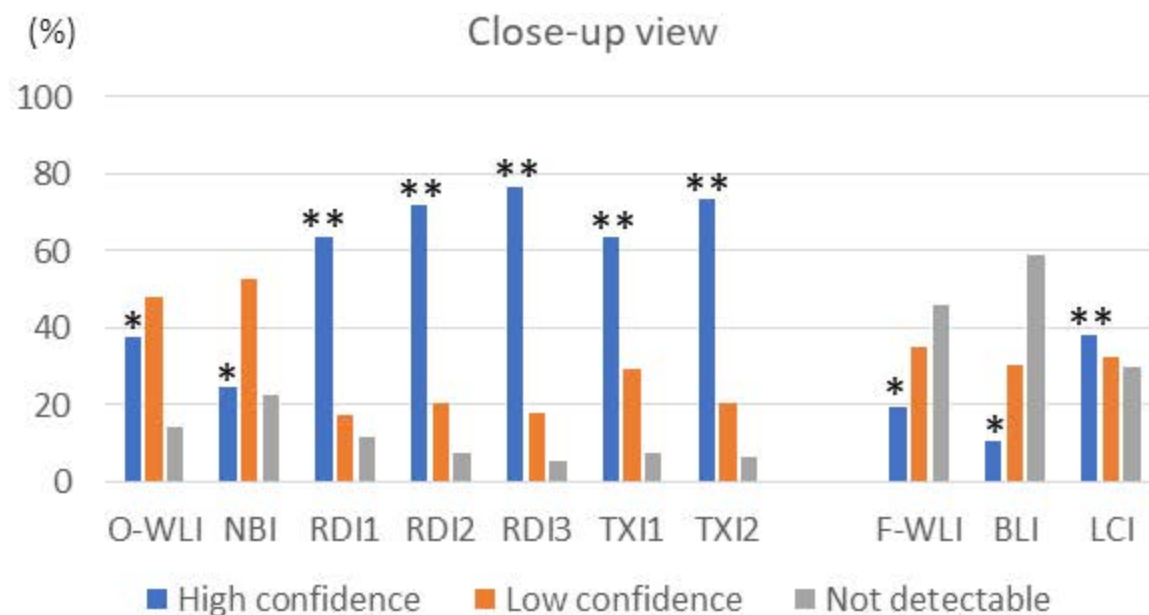
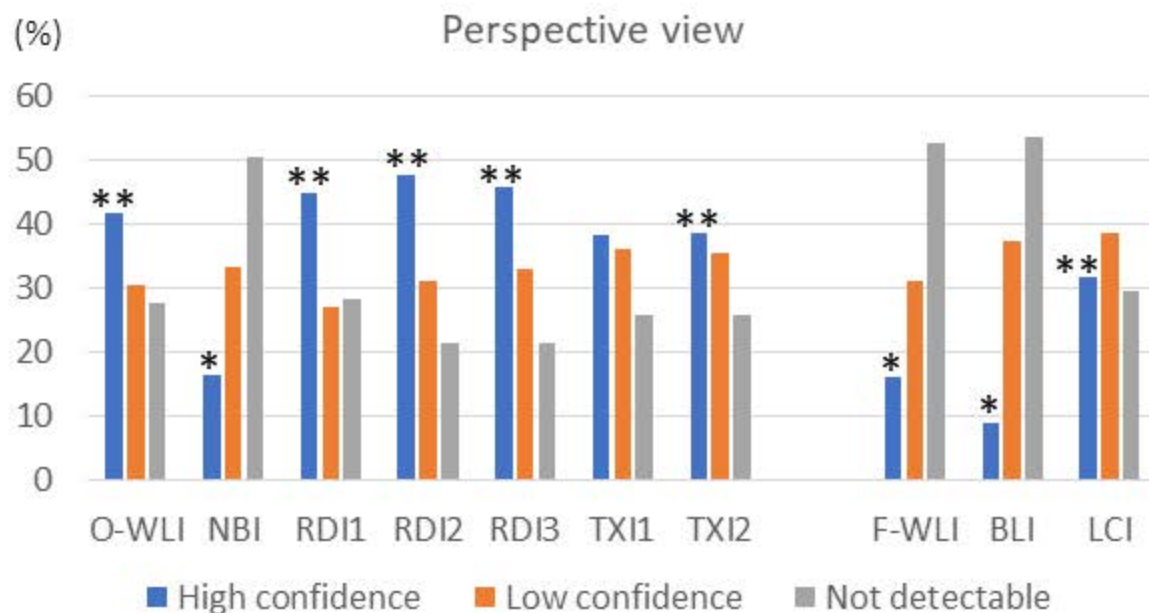


Figure 5

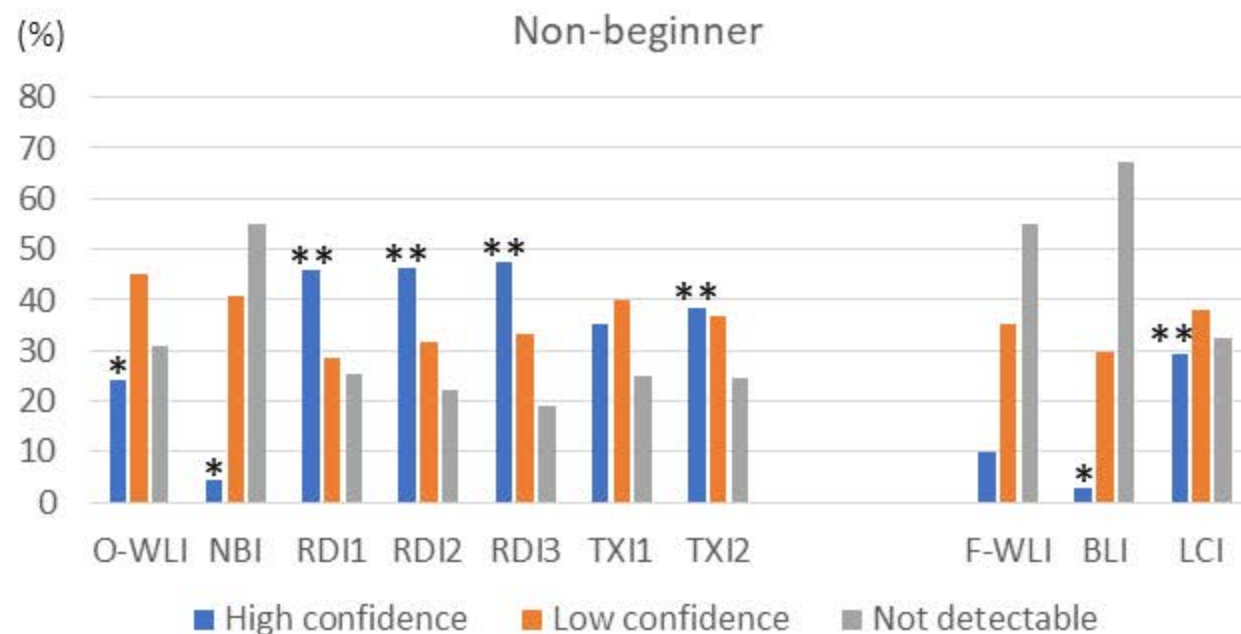
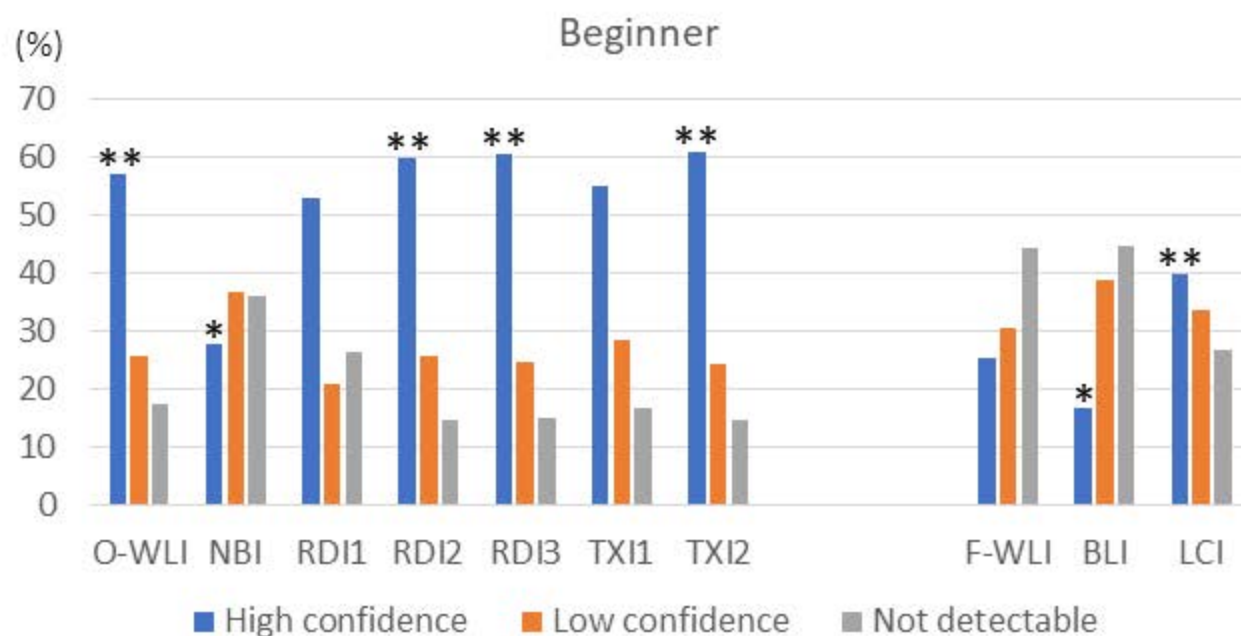


Figure 6

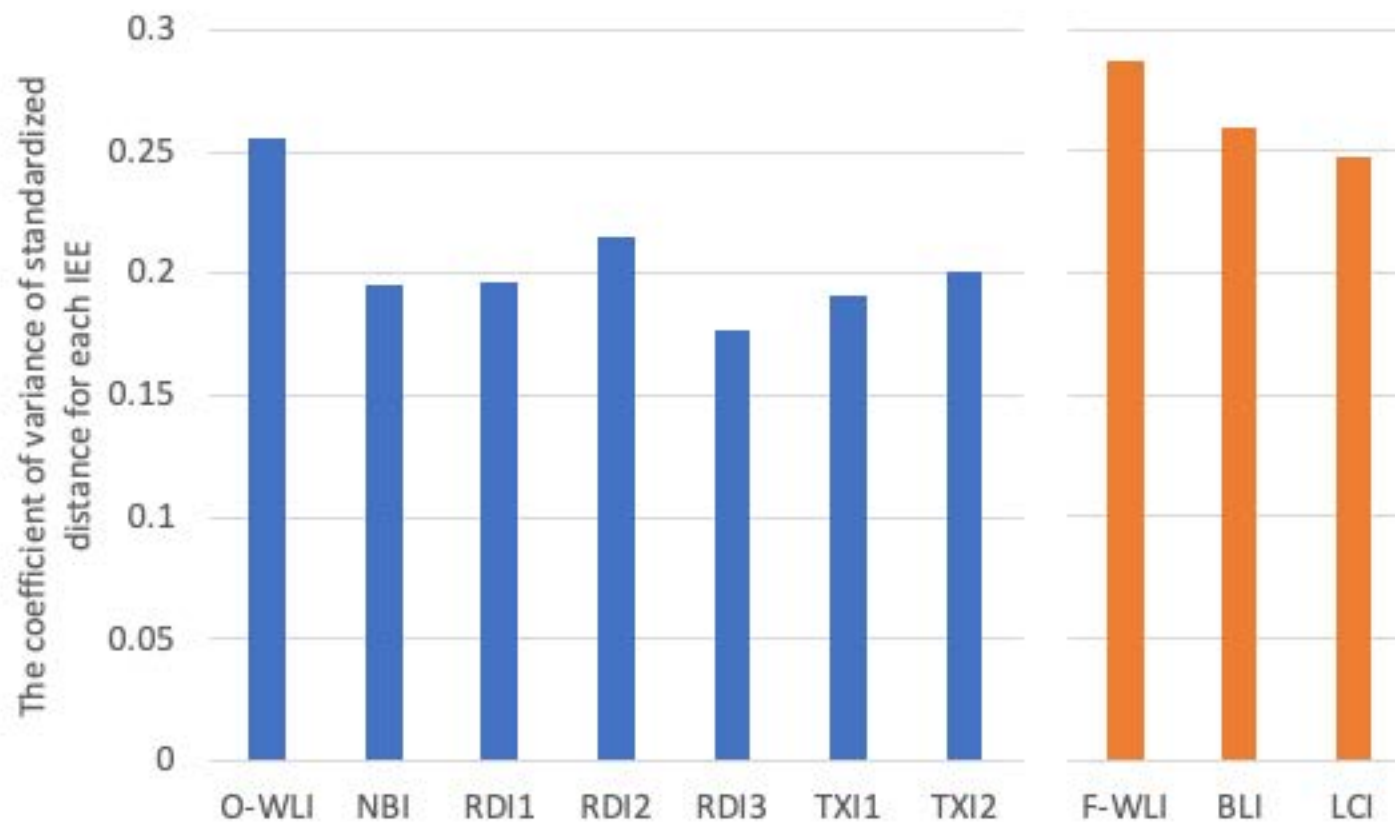


Figure 7