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Irregular coarse vessel subtypes and the biopsy-to-EUS interval differentially predict the direction of endoscopic ultrasonography misjudgment in early gastric cancer

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Research Article

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Abstract

Background: Endoscopic ultrasonography (EUS) is widely used for accuracy for depth assessment of early gastric cancer (EGC). Irregular coarse vessels (ICV) on magnifying endoscopy with narrow-band imaging (ME-NBI) have been suggested as a potential endoscopic sign of submucosal invasion. However, whether their significance varies by relationship to prior biopsy sites, and whether the biopsy-to-EUS interval modulates this association, has not been systematically studied. This study aimed to evaluate factors independently associated with EUS overestimation and underestimation in EGC, focusing on the differential roles of non-biopsy-derived versus biopsy-derived irregular coarse vessels and the modulating effect of the biopsy-to-EUS interval on staging accuracy.

Methods: This single-center retrospective study included 575 patients with EGC who underwent ME-NBI and EUS before endoscopic submucosal dissection. ICV were classified as non-biopsy-derived (NC-ICV) or biopsy-derived (BC-ICV) according to their relationship with prior biopsy sites. Multinomial logistic regression, interaction, stratified, and sensitivity analyses were performed.

Results: EUS findings agreed with histopathology in 397 patients (69.0%), with underestimation in 54 (9.4%) and overestimation in 124 (21.6%). NC-ICV was independently associated with underestimation (OR 8.12) and BC-ICV with overestimation (OR 8.53). Poorly differentiated histology was an independent risk factor for underestimation (OR 3.21), whereas junior endoscopists were independently associated with overestimation (OR 1.67). In interaction analysis, the overestimation risk of BC-ICV was modulated by the biopsy-to-EUS interval, being strongest at <14 days (OR 43.26) and diminishing with longer intervals, whereas NC-ICV consistently predicted underestimation across all intervals, most pronounced beyond 20 days (OR 15.23). Sensitivity analysis confirmed the robustness of these findings.

Conclusions: ICV subtype and the biopsy-to-EUS interval are independently associated with the direction of EUS misjudgment in EGC. These findings support deferring EUS to at least 3 weeks after biopsy when feasible.

Introduction

Gastric cancer remains one of the most common malignancies and a leading cause of cancer-related death worldwide. With the widespread application of screening endoscopy, an increasing proportion of gastric cancers are now detected at an early stage. Early gastric cancer (EGC), defined as carcinoma confined to the mucosa or submucosa irrespective of lymph node metastasis, can be curatively treated by endoscopic submucosal dissection (ESD) when the risk of lymph node metastasis is negligible[1, 2]. Accurate preoperative determination of invasion depth is therefore of paramount clinical importance, as it directly determines whether a patient is eligible for endoscopic resection or requires radical gastrectomy.

Endoscopic ultrasonography (EUS) is widely used for predicting the depth of invasion of EGC. However, reported diagnostic accuracy varies considerably across studies, ranging from approximately 55% to

87%[3–9]. Both directions of misjudgment can occur: overestimation may lead to unnecessary radical surgery and overtreatment, whereas underestimation may result in incomplete endoscopic resection and undertreatment. Several lesion-related factors have been shown to compromise EUS accuracy, including larger tumor size[10], undifferentiated histology[10, 11], and ulceration[5, 11].

However, several clinically relevant questions remain to be addressed. First, current guidelines recommend EUS for pretreatment staging of EGC, but none specifies the optimal timing of EUS relative to endoscopic biopsy[12–14]. Because forceps biopsy is required for the diagnosis of EGC, EUS is invariably performed afterwards, yet no standardized biopsy-to-EUS interval has been established. Whether this interval affects staging accuracy has not been systematically investigated. Second, abnormal vascular patterns on magnifying endoscopy with narrow-band imaging (ME-NBI), including dilation, tortuosity, and variation in shape, are associated with early gastric cancer and submucosal invasion[15–17]. We term such vessels irregular coarse vessels (ICV). However, we have observed in our own clinical practice that ICV may also arise in the mucosa adjacent to previous biopsy sites. Whether these biopsy-derived ICV similarly indicate submucosal invasion remains unknown.

The aims of this study were to classify ICV detected by ME-NBI into non-biopsy-derived (NC-ICV) and biopsy-derived (BC-ICV) subtypes according to their relationship with prior biopsy sites, and to evaluate whether ICV subtype and the biopsy-to-EUS interval independently predict and interactively modify the direction of EUS misjudgment in staging the depth of invasion of EGC. The findings are expected to aid the interpretation of ME-NBI and EUS images and to inform the optimal timing of EUS relative to endoscopic biopsy in clinical practice.

Methods

Study population

This single-center retrospective study consecutively enrolled 575 patients with early gastric mucosal lesions from January 2020 to December 2025 at the Fourth Hospital of Hebei Medical University. All patients underwent preoperative routine gastroscopy with biopsy, NBI-ME examination, and EUS. All lesions were treated by ESD, and postoperative pathological results were regarded as the gold standard. The study involving human participants was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University (approval no. 2024KY230). All procedures were performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments, as well as local institutional requirements. Written informed consent was obtained from all individual participants included in the study.

Inclusion and exclusion criteria

1. **Inclusion criteria**: (1) Preoperative biopsy confirmed high-grade gastric intraepithelial neoplasia (HGIN) or early gastric cancer; (2) Standardized preoperative NBI-ME examination with complete and interpretable images for vascular morphological evaluation; (3) Preoperative EUS examination

performed for depth assessment; (4) Patients who met the ESD indications for early gastric cancer and underwent successful ESD; (5) Complete clinical, endoscopic, imaging, and pathological data.

2. **Exclusion criteria**: (1) Blurred, severely reflective, or visually obstructed endoscopic images that failed vascular classification and lesion evaluation; (2) A history of gastric surgery, radiotherapy, chemotherapy treatment; (3) Complicated with advanced gastric cancer, other gastrointestinal malignancies, or severe organic gastric diseases; (4) Incomplete pathological or follow-up data; (5) Lesions with endoscopic ulcerative changes (including active ulcer, healing ulcer, and ulcer scar).

Preoperative endoscopic preparation

All patients fasted for more than 6 hours before endoscopy. To facilitate clear observation of the mucosal surface and eliminate mucus and foam, patients orally ingested a combined mucolytic and defoaming solution 10 minutes before the procedure. The solution consisted of 100 mL warm water containing 20,000 units of streptokinase (Tide Pharmaceutical, Beijing, China) and 5 g of dimethicone powder (Honghe Pharmaceutical, Sichuan, China). This standardized preparation ensured high-quality visualization of mucosal microvessels and lesion margins during NBI-ME observation.

Endoscopic equipment and standard operating procedures

1) Magnifying endoscopy equipment: All NBI-ME examinations were performed using a GIF-H260Z magnifying gastroscope (Olympus Medical, Tokyo, Japan) with optical magnification and narrow-band imaging functions.

2) Standard NBI-ME procedure: All patients were placed in the left lateral decubitus position. After routine insertion to the duodenum, retrograde observation of the entire gastric cavity was performed under white light mode to identify target lesions. Subsequently, the mode was switched to NBI, and optical magnification was applied to focus on the lesion and the surrounding 5 mm mucosal area to clearly visualize microvascular architecture and microsurface patterns. High-definition images of the lesion center, lesion margin, and adjacent normal mucosa were captured for subsequent morphological classification. All NBI-ME examinations were performed strictly in accordance with unified standardized protocols by experienced endoscopists to ensure consistent operation and high-quality image acquisition.

3) Standard EUS procedure: EUS examination was performed immediately after NBI-ME evaluation. A high-frequency ultrasonic probe was applied with degassed water filling to ensure adequate mucosal contact and avoid bubble interference. Multi-angle scanning was performed to visualize lesion layers, boundaries, thickness, and surrounding mucosal structures. Special attention was paid to distinguishing intramucosal lesions from submucosal invasion. Preoperative EUS depth staging was recorded and compared with postoperative pathological results to define underestimation, overestimation, and consistent diagnosis.

Surgical indications for ESD

The ESD indications in this study were based on the 2018 expert consensus on standardized endoscopic resection for early gastric cancer[18]. **Absolute indications:** (1) Ulcer-free differentiated intramucosal carcinoma (cT1a); (2) Differentiated intramucosal carcinoma (cT1a) with ulceration and lesion size ≤3 cm; (3) High-grade gastric intraepithelial neoplasia (HGIN). **Expanded indication:** Ulcer-free undifferentiated intramucosal carcinoma (cT1a) with lesion size ≤2 cm. Because ulceration is a well-established confounder that compromises EUS staging accuracy[5, 11], lesions with ulcerative changes were excluded from the final analysis; consequently, the study population was limited to non-ulcerated early gastric cancer. Postoperative surveillance was scheduled at 3, 6, and 12 months after ESD, followed by annual endoscopic review.

Image screening and quality control

All archived endoscopic images were independently and blindly reviewed by two experienced endoscopists, who classified the morphology of irregular coarse vessels on NBI-ME and determined lesion boundaries and morphological features without knowledge of clinical data, EUS findings, or final pathology. Images were screened according to uniform criteria, and those with severe blurring, marked mucus accumulation, or prominent light reflection obscuring the vessels were excluded. Discrepancies between the two reviewers were resolved by a third, more senior endoscopist. To assess inter-observer agreement, 80 images were randomly selected from the 575 enrolled cases and independently reviewed by the two endoscopists. The inter-observer agreement for the classification of irregular coarse vessels was substantial (Cohen's kappa = 0.685, 95% CI: 0.499–0.871; P < 0.001), supporting the reliability of the image-based assessment.

Variable definition and classification

The outcome variable was EUS depth diagnostic error, categorized as underestimation, overestimation, and consistent diagnosis (reference group). Independent variables included **endoscopist experience level**, lesion size, lesion boundary morphology, lesion classification, pathological differentiation, gastric cystic gastritis grade, biopsy number, biopsy-EUS interval and NBI-ME irregular coarse vessel (ICV) classification. The biopsy-EUS interval was stratified into three subgroups:≤14 days, 14-20 days, and >20 days.

1. Endoscopist experience stratification criteria: All endoscopists who performed NBI-ME and EUS examinations were stratified by years of independent endoscopic practice. Junior endoscopists were defined as those with fewer than 5 years of independent EUS experience, while senior endoscopists were defined as those with 5 years or more of independent EUS experience.

2. Classification and description of NBI-ME irregular coarse vessels

On ME-NBI, ICV were defined as vascular structures within the lesion characterized by dilation (caliber ≥1.5 times that of reference microvessels), tortuosity (twisted or bent course), and variation in shape (highly variable shape and size), which were morphologically distinct from the fine reticular microvessels

of the surrounding normal mucosa. Based on the spatial relationship between the abnormal vascular area and previous biopsy sites, ICV were classified into two subtypes, namely non-biopsy-derived (NC-ICV) and biopsy-derived (BC-ICV), and lesions without ICV served as the control group for subsequent analyses:

1. **Non-biopsy-derived irregular coarse vessel (NC-ICV)**: NC-ICV were morphologically characterized by dilation, tortuosity, and variation in shape within the lesion, without spatial overlap with previous biopsy sites (Figure 1).
2. **Biopsy-derived irregular coarse vessel (BC-ICV)**: BC-ICV presented as focal dilation, tortuosity, and variation in shape, spatially confined to previous biopsy sites and adjacent mucosal areas (Figure 2).
3. **No irregular coarse vessel (No ICV)**: Regular and uniform microvascular architecture without dilation, tortuosity, or variation in shape.

The NC-ICV/BC-ICV classification was a purely morphological categorization based on the relationship between coarse vessels and previous biopsy sites, without presupposing their histologic nature.

Statistical analysis

All statistical analyses were performed using SPSS 21.0 software. With postoperative pathology as the gold standard, preoperative EUS depth diagnosis was categorized into underestimation, overestimation, and consistent diagnosis, and the consistent group was set as the reference. Multinomial logistic regression models were used to screen independent risk factors for EUS depth misjudgment. A fully adjusted main-effect model was constructed by incorporating lesion size, endoscopist experience level, lesion classification, pathological differentiation, lesion boundary, NBI-ME irregular coarse vessel type, biopsy-EUS interval, and number of biopsy specimens. Subsequently, the interaction term of irregular coarse vessel type × biopsy-EUS interval was added to evaluate the interactive effect on diagnostic errors. Stratified simple effect analysis was conducted in three subgroups (<14 days, 14–20 days, and >20 days) to explore the heterogeneous effects of NC-ICV and BC-ICV on EUS misjudgment across different time windows. Sensitivity analysis was performed by treating the biopsy-EUS interval as a continuous variable to verify the robustness of the primary results. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for all models. A two-tailed P value < 0.05 indicated statistical significance.

Results

Baseline Characteristics

A total of 575 patients were enrolled, of whom 397 (69.0%) had EUS depth assessment consistent with the histopathologic diagnosis, 54 (9.4%) were underestimated, and 124 (21.6%) were overestimated (Table 1). Significant between-group differences were observed for lesion size (P = 0.006), histologic differentiation (P = 0.003), lesion boundary (P < 0.001), NBI-ME irregular coarse vessel type (P < 0.001), biopsy-to-EUS interval (P = 0.012), and number of biopsy specimens (P = 0.017). No significant

differences were found in sex, age, endoscopist experience level, macroscopic type, lesion location, gastric wall site, or gastric cystic gastritis (all P > 0.05). Specifically, lesions ≥2 cm were more frequently overestimated than those <2 cm (27.9% vs. 18.3%). Poorly differentiated lesions showed higher rates of both underestimation (20.59%) and overestimation (35.29%) compared with well-to-moderately differentiated lesions (8.69% and 20.70%). Lesions with irregular boundaries were more frequently overestimated (30.37%) and underestimated (13.08%) than those with regular boundaries (16.34% and 7.20%). Regarding irregular coarse vessels, NC-ICV was predominantly associated with underestimation (35.44%), whereas BC-ICV was highly concentrated in the overestimation group (62.82%); lesions without irregular coarse vessels were accurately staged in 79.67% of cases. Overestimation was most frequent when the biopsy-to-EUS interval was <14 days (31.51%) and declined progressively with longer intervals. Overestimation was also more common in lesions with >2 biopsy specimens than in those with ≤2 (30.34% vs. 19.96%).

Multivariable Logistic Regression

Multivariable multinomial logistic regression revealed distinct risk profiles for the two directions of misjudgment (Table 2). NC-ICV (OR = 8.12, 95% CI: 4.07–16.20, P < 0.001) and poorly differentiated histology (OR = 3.21, 95% CI: 1.03–10.01, P = 0.045) were independent risk factors for underestimation. BC-ICV was an independent risk factor for overestimation (OR = 8.53, 95% CI: 4.73–15.39, P < 0.001). A regular lesion boundary was independently associated with a lower risk of overestimation (OR = 0.48, 95% CI: 0.30–0.78, P = 0.003). A biopsy-to-EUS interval of <14 days independently increased the risk of overestimation (OR = 2.33, 95% CI: 1.21–4.46, P = 0.011). Junior endoscopists were more likely to overestimate the invasion depth than senior endoscopists (OR = 1.67, 95% CI: 1.05–2.68, P = 0.031). Poorly differentiated histology also showed a borderline association with overestimation (OR = 2.46, 95% CI: 0.88–6.85, P = 0.086). In contrast, lesion size, macroscopic type, lesion location, and the number of biopsy specimens were not independent predictors in the multivariable model.

Interaction Analysis

The interaction analysis between irregular coarse vessel type and biopsy-to-EUS interval showed a marked time-dependent pattern (Table 3 Figure 3). For underestimation, NC-ICV remained a significant risk factor across all three interval strata (<14 days: OR = 7.19, 95% CI: 1.87-27.73, P = 0.004; 14-20 days: OR = 6.49, 95% CI: 2.04-20.63, P = 0.002; >20 days: OR = 15.23, 95% CI: 4.09-56.73, P < 0.001). For overestimation, the effect of BC-ICV was strongest at an interval of <14 days (OR = 43.26, 95% CI: 12.49-149.83, P < 0.001), remained significant at 14-20 days (OR = 9.33, 95% CI: 3.22-27.09, P < 0.001), but was no longer significant beyond 20 days (OR = 2.55, 95% CI: 0.80-8.16, P = 0.114). In the interaction model, a regular boundary (OR = 0.51, 95% CI: 0.31-0.84, P = 0.008) and junior endoscopists (OR = 1.63, 95% CI: 1.01-2.64, P = 0.045) remained independently associated with overestimation, and poorly differentiated histology was independently associated with underestimation (OR = 3.38, 95% CI: 1.07-10.69, P = 0.038).

Stratified Analysis

The stratified simple effect analysis confirmed the above findings (Table 4 Figure 4). At an interval of <14 days, NC-ICV was significantly associated with underestimation (OR = 15.88, 95% CI: 2.28-110.84, P = 0.005), and BC-ICV was strongly associated with overestimation (OR = 68.14, 95% CI: 13.51-343.82, P < 0.001). At 14-20 days, both associations persisted (NC-ICV for underestimation: OR = 5.54, 95% CI: 2.01-15.27, P = 0.001; BC-ICV for overestimation: OR = 8.92, 95% CI: 3.39-23.47, P < 0.001). Beyond 20 days, NC-ICV remained strongly associated with underestimation (OR = 32.86, 95% CI: 6.43-168.04, P < 0.001), whereas the association between BC-ICV and overestimation was no longer significant (OR = 3.45, 95% CI: 0.93-12.89, P = 0.065).

Sensitivity Analysis

In the sensitivity analysis in which the biopsy-to-EUS interval was treated as a continuous variable, the results remained consistent with the primary analysis (Table 5). The interval itself was not significantly associated with either underestimation (OR = 0.99, 95% CI: 0.96–1.02, P = 0.351) or overestimation (OR = 0.99, 95% CI: 0.96–1.01, P = 0.212). NC-ICV remained an independent risk factor for underestimation (OR = 8.23, 95% CI: 4.13–16.37, P < 0.001), and poorly differentiated histology also remained an independent risk factor for underestimation (OR = 3.47, 95% CI: 1.12–10.79, P = 0.031). BC-ICV remained an independent risk factor for overestimation (OR = 8.58, 95% CI: 4.83–15.24, P < 0.001). A regular boundary (OR = 0.48, 95% CI: 0.30–0.78, P = 0.003) and junior endoscopists (OR = 1.69, 95% CI: 1.06–2.69, P = 0.028) were also independently associated with overestimation. The consistency of effect directions and significance across the primary and sensitivity analyses supports the robustness of our model.

Discussion

Accurate assessment of invasion depth is essential for treatment selection in EGC, and EUS is widely used for this purpose; however, its diagnostic performance remains suboptimal. In the present study of 575 patients with EGC, irregular coarse vessels identified by ME-NBI were categorized according to their relationship with previous biopsy sites. NC-ICV were independently associated with underestimation, whereas BC-ICV were independently associated with overestimation, and these associations were modulated by the biopsy-to-EUS interval. These findings highlight the importance of integrating biopsy history and ME-NBI vascular findings into EUS interpretation and support optimizing the timing of EUS relative to biopsy to improve staging accuracy.

In the present study, EUS achieved an overall concordance rate of 69.0% with histopathologic depth of invasion, which is largely consistent with previous reports[4, 19–22]. Notably, the direction of misjudgment in our cohort, with underestimation in 9.4% and overestimation in 21.6%, closely paralleled the findings of Yanai et al. (underestimation 7.4%, overestimation 24.1%)[23], confirming that overestimation is a systematic and more frequent error than underestimation in the EUS staging of EGC. This systemic bias may arise because EUS cannot reliably distinguish tumor-associated inflammation, peritumoral fibrosis, or tangential scanning artifacts from true neoplastic infiltration. Given that nearly one-third of patients in

our cohort had inaccurate staging, over-reliance on EUS alone for treatment decisions carries a substantial risk of either aggressive overtreatment or inadequate resection.

Poorly differentiated histology was an independent risk factor for EUS underestimation, consistent with previous evidence that poor differentiation compromises EUS staging accuracy [10, 11]. The underlying mechanism may relate to the infiltrative growth pattern characteristic of poorly differentiated carcinoma, in which tumor cells invade the submucosa as scattered single cells or small nests rather than as a cohesive mass; such microscopic infiltration is sonographically undetectable and thus prone to underestimation. In addition, junior endoscopists were independently associated with overestimation compared with senior endoscopists. EUS is an operator-dependent procedure, and its diagnostic accuracy has been shown to improve with the experience of the endoscopist[24]. In a study evaluating EUS for distinguishing mucosal from submucosal invasion, accuracy improved from 60.6% in the first year of practice to 75.0% in the second year, with 44.2% of mucosal cancers overstaged as submucosal invasion [25]. A CUSUM-based learning curve analysis similarly showed significantly lower T-staging accuracy in trainees than in senior experts [26]. It is therefore plausible that less experienced endoscopists, being more vigilant about the risk of missing deep invasion, tend to interpret equivocal sonographic findings as submucosal involvement and thus consciously overestimate the invasion depth. These observations highlight the operator-dependent nature of EUS staging and underscore the importance of endoscopist experience in the accurate preoperative evaluation of EGC.

Regarding lesion boundary, a regular boundary was inversely associated with EUS overestimation, indicating that an irregular boundary significantly increased the risk of overestimation. In the present study, an irregular boundary was defined as a lesion margin exhibiting moth-eaten, saw-toothed, or tentacle-like extensions. We speculate that such irregular margins reflect eccentric tumor growth. During the examination, the center of the lesion may not have been scanned, so perpendicular scanning of the lesion may not have been achieved. Oblique scanning could then distort the layered architecture of the gastric wall, resulting in spurious thickening and consequent overestimation. This hypothesis warrants further validation in future studies.

Multivariate analysis identified NC-ICV as an independent risk factor for EUS underestimation. In contrast to the interval-dependent effect of BC-ICV, the interaction analysis showed that the underestimation risk conferred by NC-ICV was significant across all interval subgroups, including intervals of less than 14 days, 14 to 20 days, and more than 20 days. The stratified analysis further confirmed that NC-ICV remained a stable risk factor for underestimation regardless of the interval, with the association being most prominent when the interval was long. The sensitivity analysis, in which the interval was treated as a continuous variable with full adjustment for potential confounders, yielded consistent results, supporting the robustness and stability of our model.

Abnormal vascular patterns on NBI-ME, including dilated vessels, tortuosity, and variation in shape, have been associated with both the diagnosis of early gastric cancer and submucosal invasion[15–17, 27]. In the present study, NC-ICV was distributed in the central or marginal area of the lesion without overlapping

previous biopsy sites, reflecting inherent tumor-related microvascular abnormalities rather than biopsy-induced alterations. Although NC-ICV may therefore reflect a tendency toward deeper invasion, EUS is not sufficiently sensitive for the detection of minute submucosal invasion. Previous studies have shown that EUS has a relatively low accuracy in predicting SM1/SM2 invasion, with some reporting an accuracy of less than 50%, and that EUS has limited accuracy for minute submucosal invasion [9, 28, 29]. This insensitivity of EUS to microinvasion may, at least in part, account for the underestimation observed in lesions harboring NC-ICV.

The time-independence of this underestimation risk further supports the above interpretation, as NC-ICV, unlike biopsy-related reparative changes that subside with healing, represents tumor-associated vascular abnormalities that persist regardless of the biopsy-to-EUS interval. Clinically, irregular coarse vessels arising in non-biopsy areas on NBI-ME therefore deserve close attention: even when EUS shows no definite submucosal invasion, their presence warrants caution, since underestimation and deeper invasion cannot be reliably excluded. Such lesions require careful evaluation and appropriate treatment planning to avoid undertreatment.

Multivariate analysis identified BC-ICV and a biopsy-to-EUS interval of less than 14 days as independent risk factors for EUS overestimation. The interaction analysis further demonstrated that the overestimation risk conferred by BC-ICV was strongly modulated by the interval: it was most pronounced when the interval was shorter than 14 days, remained significant at 14 to 20 days, and was no longer significant when the interval exceeded 20 days. The stratified analysis confirmed this time-dependent pattern, showing that the association between BC-ICV and overestimation was strongest under short intervals and diminished progressively as the interval lengthened. The sensitivity analysis, in which the interval was treated as a continuous variable with full adjustment for potential confounders, yielded consistent results, supporting the robustness and stability of our model.

These findings are supported by the pathophysiology of post-biopsy mucosal healing. First, studies in humans and animal models have shown that a mucus clot forms over a mucosal defect within days, that regenerating mucosa grows from the defect margin at 2 weeks, and that neovascularization supports coverage of the entire defect[30]. Notably, even the re-epithelialized mucosa of a healed ulcer has been shown to retain histologic and ultrastructural abnormalities, including a disorganized microvascular network[31]. The reparative neovasculature arising at biopsy sites may therefore constitute the morphological basis of the irregular coarse vessels, i.e., BC-ICV. Second, forceps biopsy creates an acute mucosal defect that follows the well-characterized sequence of erosion-to-ulcer progression. In experimental models, gastric erosions peak at 12 hours after injury, decline by 24 hours, these erosions progressed at day 3 into deeper ulcers whose area declined progressively within the next 5–15 days[32]. The presence of ulceration and inflammatory changes at a recent biopsy site may predispose to EUS overstaging when the examination is performed within a short interval after biopsy[11, 33].

Current guidelines for the management of gastric cancer recommend EUS for preoperative staging but provide no recommendation on the timing of EUS relative to endoscopic biopsy (refs), indicating that no

standard interval has been established[12–14, 34]. Given that the overestimation risk associated with BC-ICV was no longer significant when the interval exceeded 20 days, we suggest that EUS be performed at least 21 days (3 weeks) after endoscopic biopsy whenever clinically feasible, to minimize the confounding effect of biopsy-related inflammatory and reparative changes and to avoid unnecessary aggressive treatment. This recommendation, however, warrants further prospective validation.

Several limitations should be acknowledged. First, this was a single-center retrospective study, and the biopsy-to-EUS interval was determined by clinical practice rather than randomization, which may have introduced selection and indication bias. Second, EUS depth assessment relied on static images retrieved from the historical database, which lacked real-time dynamic evaluation and may have limited assessment of the entire lesion. Third, the underestimation group was relatively small (n = 54), limiting the statistical power of some subgroup analyses. Fourth, the proposed reparative-neovascular interpretation of BC-ICV was inferred from published healing data rather than directly validated in resected specimens, and warrants future histopathologic confirmation with microvascular markers. Finally, although inter-observer agreement was substantial (kappa = 0.685), the reproducibility of this classification across different centers and endoscopists remains to be determined. Despite these limitations, the consistency of the main findings across multivariable adjustment and multiple sensitivity analyses supports the robustness of our conclusions.

In conclusion, in patients with EGC undergoing EUS before endoscopic resection, the subtype of ICV on ME-NBI and the biopsy-to-EUS interval are independently associated with the direction of EUS misjudgment. NC-ICV independently predicted underestimation, whereas BC-ICV independently predicted overestimation, with the latter being most pronounced when EUS was performed within 14 days after biopsy and diminishing as the interval lengthened. These findings highlight the importance of interpreting ICV in the context of biopsy history and support delaying EUS for at least 3 weeks after biopsy to reduce overestimation.

Abbreviations

EUS, endoscopic ultrasonography;

ME-NBI, magnifying endoscopy with narrow-band imaging;

ICV, irregular coarse vessels;

BC-ICV, biopsy-derived irregular coarse vessels;

NC-ICV, non-biopsy-derived irregular coarse vessels;

EGC, early gastric cancer;

ESD, endoscopic submucosal dissection;

OR, odds ratio;

CI, confidence interval.

Declarations

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Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University (2024KY230). Informed consent was obtained from all participants to participate in this study. This study strictly adhered to the ethical standards outlined in the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Authors’ contributions

Lei Zhang, Nana An designed the study; Lei Zhang, Nana An, Limian Er, Xiuli Zheng, Honghai Guo and Juntao Lu collected and analyzed the data; Nana An wrote the main manuscript; Lei Zhang and Limian Er

critically revised the manuscript. All authors reviewed the manuscript. The author(s) read and approved the final manuscript.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request without breaching participant confidentiality.

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Tables

Table 1. Demographic and clinical characteristics of the enrolled patients (N = 575)

Characteristic	Total (n)	Consistent (n = 397)	Underestimation (n = 54)	Overestimation (n = 124)	P-value
Sex, n (%)					0.692
Male	446	304 (68.16)	41 (9.19)	101 (22.65)	
Female	117	81 (69.23)	13 (11.11)	23 (19.66)	
Age, years, n (%)					0.224
<65	269	186 (69.14)	20 (7.43)	63 (23.42)	
≥65	294	199 (67.69)	34 (11.56)	61 (20.75)	
Endoscopist experience level, n (%)					0.144
Junior	212	139 (65.57)	18 (8.49)	55 (25.94)	
Senior	363	258 (71.07)	36 (9.92)	69 (19.01)	
Lesion size, cm, n (%)					0.006
≥2	186	112 (60.21)	21 (11.29)	53 (27.90)	
<2	389	285 (73.26)	33 (8.48)	71(18.26)	
Macroscopic type, n (%)					0.073
	26	15 (57.69)	4 (15.38)	7 (26.93)	
a	72	47 (65.28)	8 (11.11)	17 (23.61)	
b	28	26 (92.86)	0 (0.00)	2 (3.7.14)	
a+c	100	69 (57.00)	14 (14.00)	17 (17.00)	
c	349	240 (68.77)	28 (8.02)	81 (23.21)	
Lesion location, n (%)					0.477
Cardia	401	274 (68.33)	42 (10.47)	85 (21.20)	
Gastric body	96	67 (69.79)	9 (9.38)	20 (20.83)	
Gastric antrum	78	56 (71.79)	3 (3.85)	19 (24.36)	
Lesion site (gastric wall), n (%)					0.353
Lesser curvature	287	195 (67.94)	27 (9.41)	65 (22.65)	
Greater curvature	55	45 (81.82)	1 (1.82)	9 (16.36)	
Anterior wall	61	41 (67.21)	6 (9.84)	14 (22.95)	
Posterior wall	172	116 (67.44)	20 (11.63)	36 (20.93)	

Characteristic	Total (n)	Consistent (n = 397)	Underestimation (n = 54)	Overestimation (n = 124)	P-value
Histological differentiation, n (%)					0.003
Well/moderately differentiated	541	382 (70.61)	47 (8.69)	112 (20.70)	
Poorly differentiated	34	15 (44.12)	7 (20.59)	12 (35.29)	
Lesion boundary, n (%)					<0.001
Regular	361	276 (76.45)	26 (7.20)	59 (16.34)	
Irregular	214	121 (56.54)	28 (13.08)	65 (30.37)	
NBI-ME irregular coarse vessel type, n (%)					<0.001
NC-ICV	79	36 (45.57)	28 (35.44)	15 (18.99)	
BC-ICV	78	28 (35.90)	1 (1.28)	49 (62.82)	
No ICV	418	333 (79.67)	25 (5.98)	60 (14.35)	
Gastric cystic gastritis, n (%)					0.642
GCP	46	31 (67.39)	6 (13.04)	9 (19.57)	
No GCP	529	366 (69.19)	48 (9.07)	115 (21.74)	
Biopsy-EUS interval, days, n (%)					0.012
<14	146	89 (60.96)	11 (7.53)	46 (31.51)	
14-20	288	207 (71.88)	26 (9.03)	55 (19.10)	
≥20	141	101 (71.63)	17 (12.06)	23 (16.31)	
Number of biopsy specimens, n (%)					0.017
≤2	486	347 (71.40)	42 (8.64)	97 (19.96)	
≥2	89	50 (56.18)	12 (13.48)	27 (30.34)	

Table 2. Multinomial logistic regression model for risk factors of EUS depth misjudgment in early gastric cancer

Variables	Underestimation vs. Consistent			Overestimation vs. Consistent		
	OR	95%CI	P	OR	95%CI	P
Lesion size						
≥2 cm	0.88	0.45-1.74	0.719	1.34	0.83-2.17	0.239
<2 cm						
Endoscopist experience level						
Junior	0.83	0.42-1.61	0.577	1.67	1.05-2.68	0.031
Senior						
Lesion classification						
□	1.44	0.37-5.55	0.601	2.19	0.78-6.15	0.136
□a	1.44	0.57-3.62	0.441	1.75	0.88-3.49	0.110
□b	-	-	-	0.34	0.07-1.70	0.190
□a+□c	1.35	0.63-2.92	0.444	0.71	0.36-1.39	0.317
□c						
Pathological differentiation						
Moderate-well differentiated						
Poorly differentiated	3.21	1.03-10.01	0.045	2.46	0.88-6.85	0.086
Lesion boundary						
Regular boundary	0.60	0.31-1.15	0.122	0.48	0.30-0.78	0.003
Irregular boundary						
NBI-ME irregular coarse vessel type						
NC-ICV	8.12	4.07-16.20	<0.001	1.63	0.80-3.29	0.178
BC-ICV	0.43	0.06-3.32	0.416	8.53	4.73-15.39	<0.001
No ICV						
Biopsy-EUS interval						
<14	0.89	0.36-2.17	0.792	2.33	1.21-4.46	0.011
14-20	0.89	0.43-1.85	0.757	1.53	0.84-2.81	0.165
□20						

Variables	Underestimation vs. Consistent			Overestimation vs. Consistent		
Biopsy number						
≤2	0.69	0.31-1.54	0.365	0.69	0.37-1.27	0.233
2						

Table 3. Multinomial logistic regression model with irregular coarse vessel × biopsy-EUS interval interaction

Variables	Underestimation vs. Consistent			Overestimation vs. Consistent		
	OR	95%CI	P	OR	95%CI	P
NBI-ME irregular coarse vessel type × Biopsy-EUS interval interaction						
NC-ICV × <14	7.19	1.87-27.73	0.004	1.02	0.19-5.51	0.980
NC-ICV × 14-20	6.49	2.04-20.63	0.002	2.04	0.70-5.91	0.190
NC-ICV × ≥20	15.23	4.09-56.73	<0.001	3.00	0.77-11.72	0.114
BC-ICV × <14	-	-	-	43.26	12.49-149.83	<0.001
BC-ICV × 14-20	1.27	0.13-12.06	0.835	9.33	3.22-27.09	<0.001
BC-ICV × ≥20	-	-	0.998	2.55	0.80-8.16	0.114
No ICV × <14	0.89	0.26-3.08	0.849	1.48	0.64-3.40	0.361
No ICV × 14-20	1.10	0.40-3.00	0.859	1.20	0.58-2.49	0.625
No ICV × ≥20						
Endoscopist experience level						
Junior	0.82	0.42-1.61	0.569	1.63	1.01-2.64	0.045
Senior						
Lesion size						
≥2 cm	0.86	0.42-1.71	0.674	1.28	0.78-2.10	0.336
<2 cm						
Lesion classification						
Ⅰ	1.37	0.35-5.38	0.651	2.09	0.730-5.93	0.169
Ⅱa	1.41	0.56-3.57	0.459	1.72	0.86-3.44	0.123
Ⅱb	-	-	-	0.29	0.05-1.61	0.156
Ⅱa+Ⅱc	1.30	0.60-2.85	0506	0.68	0.34-1.36	0.276
Ⅱc						
Pathological differentiation						
Moderate-well differentiated						
Poorly differentiated	3.38	1.07-10.69	0.038	2.49	0.89-6.94	0.082
Lesion boundary						
Regular boundary	0.60	0.31-1.17	0.133	0.51	0.31-0.84	0.008

Variables	Underestimation vs. Consistent			Overestimation vs. Consistent		
Irregular boundary						
Biopsy number						
≤2	0.69	0.31-1.55	0.370	0.65	0.35-1.22	0.182
＞2						

Table 4. Stratified simple effect analysis of NBI-ME coarse vessels on EUS depth misjudgment.

Subgroup and Vessel Type	Underestimation vs. Consistent			Overestimation vs. Consistent		
	OR	**95% CI**	**P**	**OR**	**95% CI**	**P**
Biopsy-EUS interval: <14						
NC-ICV	15.88	2.28-110.84	0.005	0.40	0.05-2.98	0.371
BC-ICV	-	-	-	68.14	13.51-343.82	<0.001
No ICV						
Biopsy-EUS interval: 14-20						
NC-ICV	5.54	2.01-15.27	0.001	1.88	0.71-4.96	0.201
BC-ICV	0.95	0.11-8.62	0.964	8.92	3.39-23.47	<0.001
No ICV						
Biopsy-EUS interval: ＞20						
NC-ICV	32.86	6.43-168.04	<0.001	3.76	0.74-18.96	0.109
BC-ICV	-	-	0.998	3.45	0.93-12.89	0.065
No ICV						

Table 5. Sensitivity analysis: multinomial logistic regression with biopsy-EUS interval as a continuous variable.

Variables	Underestimation vs. Consistent			Overestimation vs. Consistent		
	OR	95% CI	P	OR	95% CI	P
Biopsy-EUS interval (continuous, per day)	0.99	0.96-1.02	0.351	0.99	0.96-1.01	0.212
Lesion size						
≥2 cm	0.88	0.45-1.72	0.701	1.36	0.84-2.19	0.212
<2 cm						
Endoscopist experience level						
Junior	0.85	0.43-1.65	0.623	1.69	1.06-2.69	0.028
Senior						
Lesion classification						
□	1.51	0.39-5.81	0.548	2.31	0.83-6.41	0.110
□a	1.41	0.56-3.56	0.467	1.80	0.91-3.56	0.091
□b	-	-	-	0.37	0.08-1.77	0.212
□a+□c	1.35	0.62-2.92	0.446	0.73	0.38-1.43	0.362
□c						
Pathological differentiation						
Moderate-well differentiated						
Poorly differentiated	3.47	1.12-10.79	0.031	2.48	0.89-6.91	0.081
Lesion boundary						
Regular boundary	0.56	0.29-1.08	0.083	0.48	0.30-0.78	0.003
Irregular boundary						
NBI-ME irregular coarse vessel type						
NC-ICV	8.23	4.13-16.37	<0.001	1.63	0.80-3.30	0.176
BC-ICV	0.43	0.06-3.30	0.413	8.58	4.83-15.24	<0.001
No ICV						
Biopsy number						

Variables	Underestimation vs. Consistent			Overestimation vs. Consistent		
≤2	0.69	0.31-1.54	0.366	0.69	0.38-1.27	0.239
2						

Figures

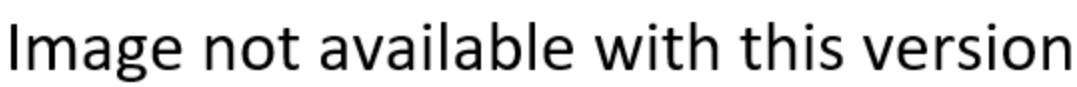


Figure 1

Representative case with NC-ICV A: A lesion on the greater curvature of the distal gastric body presenting with focal discoloration, as indicated by the black arrow. **B:** The extent of the lesion is delineated by black arrows. **C:** View under NBI-ME. Red arrows point to NC-ICV, which present as dilated, tortuous, and variation in shape within the lesion. **D:** On EUS, the submucosal layer at the lesion site appears intact. **E:** Histopathologic examination confirms poorly differentiated carcinoma with submucosal invasion to a depth of 1100 μm.

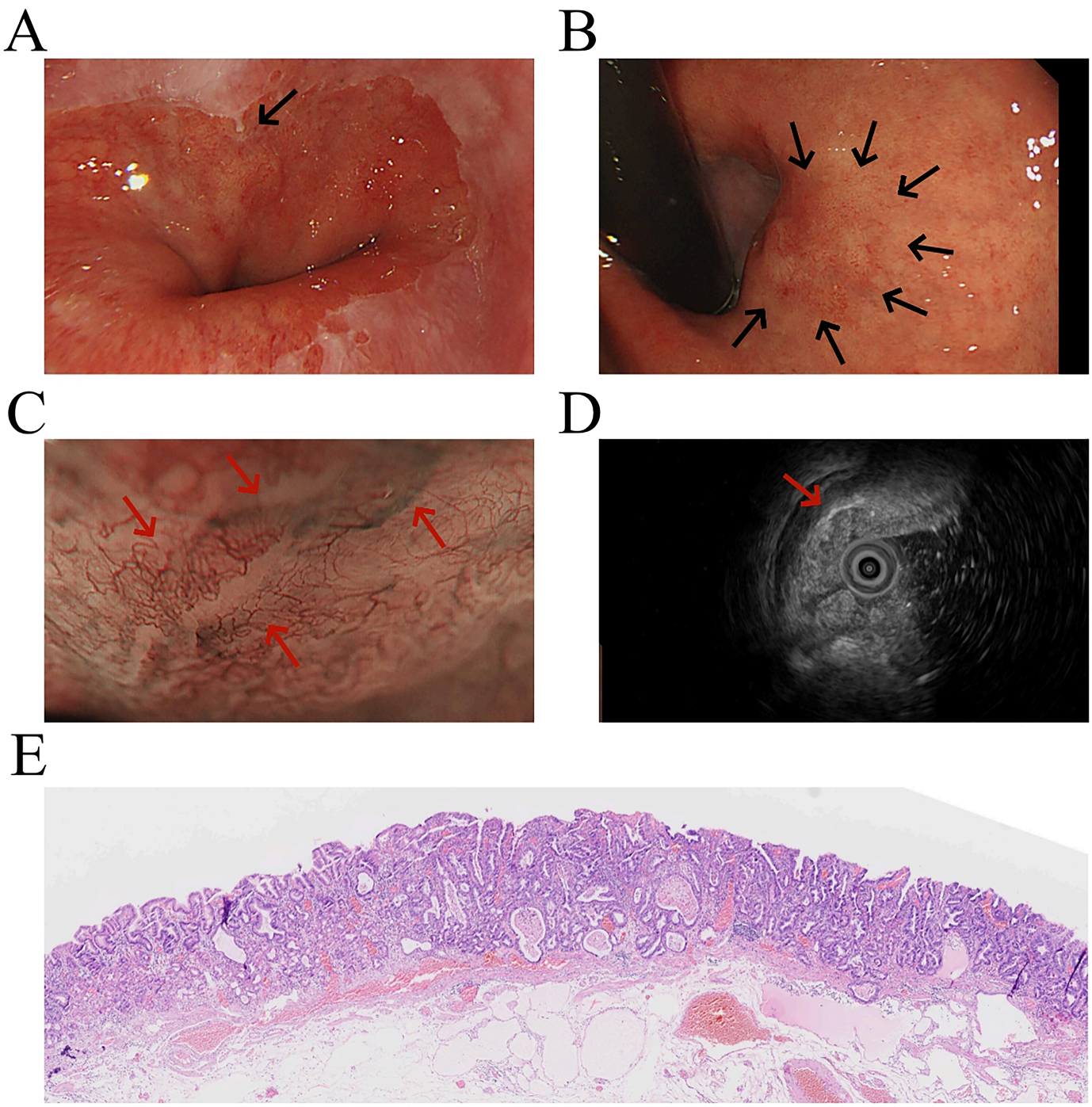


Figure 2

Representative case with BC-ICV A: A lesion on the lesser curvature of the cardia. The black arrow indicates the prior biopsy site, where white punctate reparative changes are visible, with marked hyperemia in the surrounding mucosa. **B:** The boundary of the lesion is delineated by black arrows. **C:** View under NBI-ME. Red arrows point to BC-ICV, which present as dilated, tortuous, and variation in shape within the lesion. **D:** On EUS, the red arrow marks an area with thinning of the submucosal layer. **E:** Histopathologic examination confirms tumor invasion into the muscularis mucosae.

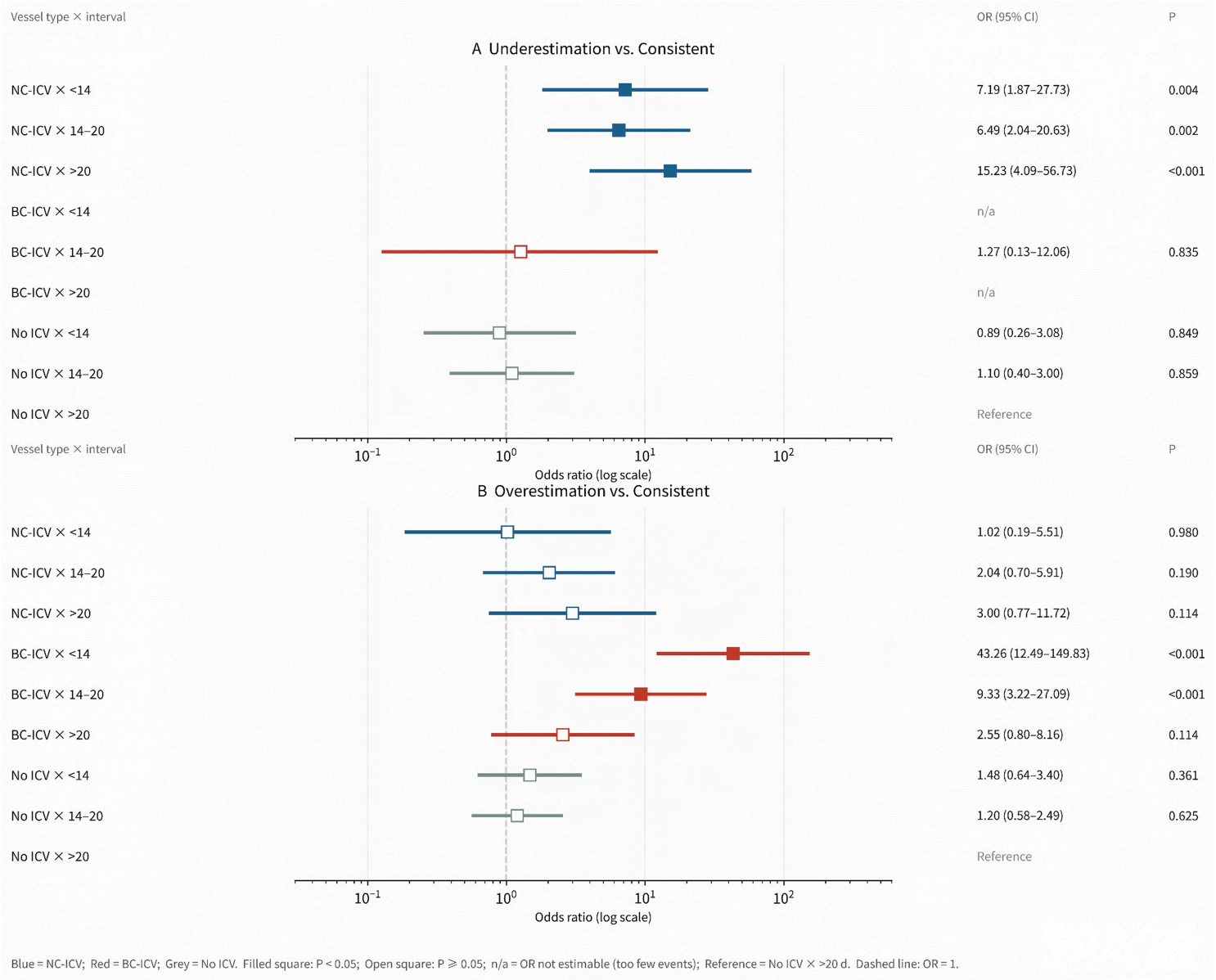


Figure 3

Forest plot of the interaction between ICV subtype and biopsy-to-EUS interval on EUS misjudgment of invasion depth in early gastric cancer. Blue squares and lines represent NC-ICV; red squares and lines represent BC-ICV; grey squares and lines represent lesions without irregular coarse vessels. Filled squares indicate P < 0.05; open squares indicate P ≥ 0.05; horizontal lines indicate 95% confidence intervals. The dashed vertical line denotes OR = 1. n/a: OR not estimable because of too few events. The reference category was no ICV at an interval of >20 days. Upper panel: underestimation; lower panel: overestimation.

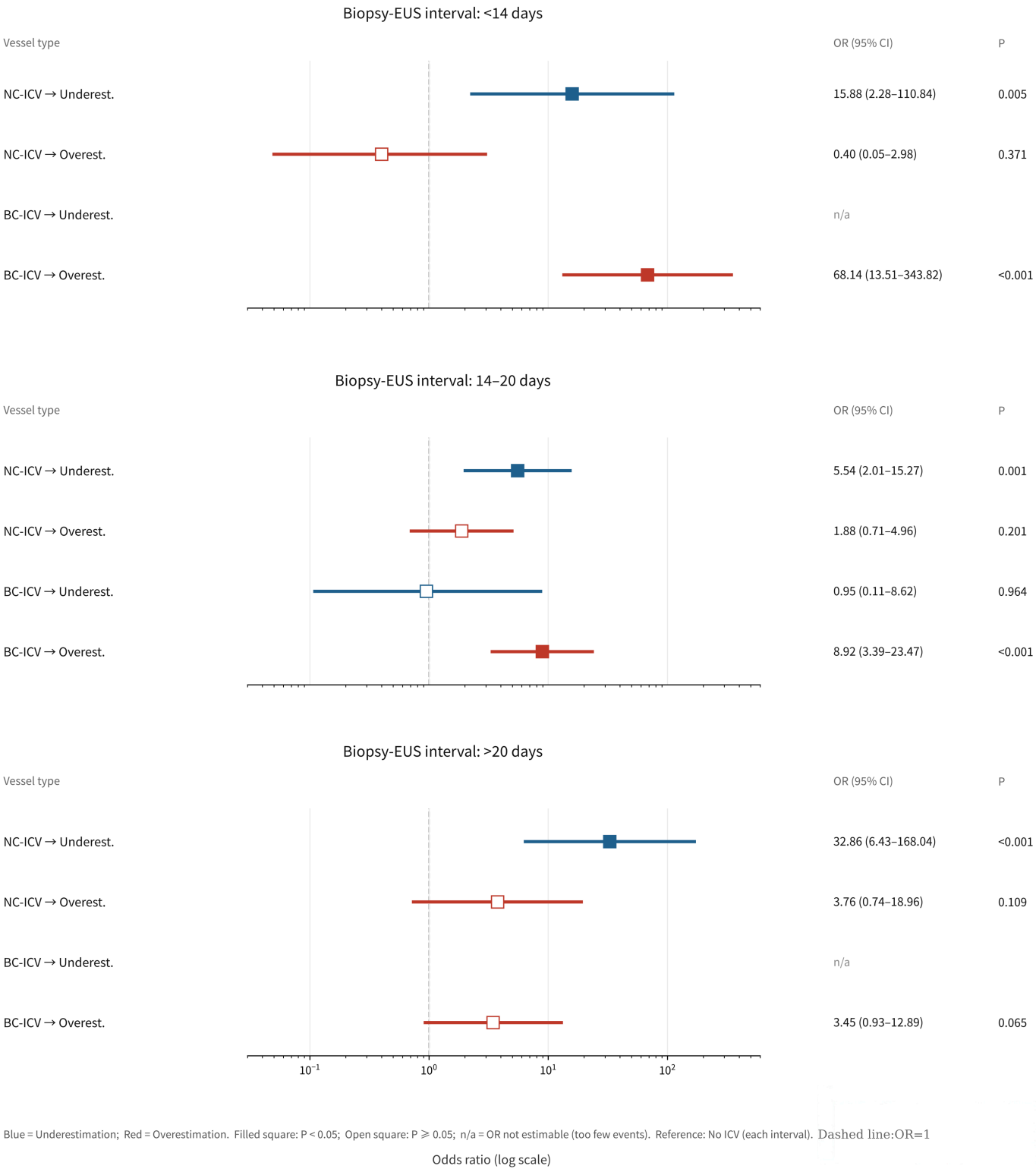


Figure 4

Stratified forest plots of the associations between ICV subtype and EUS misjudgment according to biopsy-to-EUS interval (<14 days, 14–20 days, and >20 days). Blue represents underestimation; red represents overestimation. Filled squares indicate P < 0.05; open squares indicate P ≥ 0.05; horizontal lines indicate 95% confidence intervals. The dashed vertical line denotes OR = 1. n/a: OR not estimable because of too few events. The reference category was no ICV within each interval stratum.