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Erythrocyte distribution width as a predictor of upper gastrointestinal bleeding induced by celecoxib

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Abstract: **Background**: upper gastrointestinal bleeding (UGIB) can be a serious complication of celecoxib use. At this stage, very little research has been conducted to identify potential predictors that could identify patients at an early stage. Red cell distribution width (RDW) can be considered as an existing parameter in a complete blood count that has been identified as a new potential predictor. **Objectives**: It is aimed to evaluate the ability of RDW to predict celecoxib-associated UGIB and to study its relationship to other hematological parameters. **Methods**: Four hundred patients studied were administered celecoxib retrospectively between January 2018 and August 2024. The patients were classified into non-UGIB (n=379) and UGIB (n=21) patients. UGIB patients were further subdivided depending on the amount of bleed: <250 mL, 250-400 mL, and >400 mL. We analyzed the difference in RDW, hemoglobin (Hb), Red Blood Cell Count (RBC), and Hematocrit (HCT) between the groups. The correlation between RDW and other hematology variables was assessed. The predictive value of RDW as a UGIB risk tool was assessed using the ROC Curve. **Results**: RDW values were significantly higher among patients with UGIB, while Hb, RBC, and HCT values were significantly lower compared to patients without UGIB ($P < 0.05$ for each). RDW values demonstrated substantial negative correlations with Hb ($r = -0.543$), RBC ($r = -0.525$), and HCT ($r = -0.509$). Using the ROC curve, the RDW value was found to be the most sensitive predictor of UGIB, where the sensitivity value of the threshold of 16.32% was 83.92%, and the specificity value was 60.35%, while the AUC was 0.773 (95% CI = 0.709–0.959). **Conclusion**: RDW is a unique, cost-effective biomarker that may prospectively identify patients at higher risk for the potential complications of upper gastrointestinal bleeding secondary to the use of celecoxib. However, this must await additional prospective trials.

Keywords: Celecoxib; Distribution width; Erythrocyte distribution width; Gastrointestinal hemorrhage; Hemoglobin; Predictive value; Red blood cell; Upper gastrointestinal bleeding

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INTRODUCTION

Upper gastrointestinal bleeding (UGIB) is a common gastroenterological emergency, defined as bleeding from the esophagus, stomach, duodenum, or other lesions of the upper gastrointestinal tract. UGIB presents clinically most often with melena, hematemesis, dizziness, fatigue, or other symptoms depending on the severity and duration of bleeding (Lee *et al.,* 2022). The incidence of acute UGIB in adults is around 100-180 per 100,000 population annually. Although most patients with minimal bleeding fare well with early management, the prognosis is poor in high-risk groups, such as the elderly or those with repeat bleeding or severe comorbidities, in which case mortality may be up to 30%. This serves to stress the importance of early diagnosis, prompt intervention and close monitoring (Meram *et al.,* 2024; Li *et al.,* 2023). Furthermore, the heterogeneous clinical presentation and the fulminant disease course highlight the necessity for simple, non-invasive predictive markers for early intervention to prevent potentially life-threatening complications.

The pathogenesis of UGIB is multifactorial and peptic ulcer disease, acute erosive hemorrhagic gastritis, gastric cancer, esophageal or gastric varices and Mallory-Weiss syndrome are common. Aspirin, non-steroidal anti-inflammatory agents (NSAIDs) and antiplatelet medications are increasingly being implicated as major causes (Jeong *et al.,* 2023; Guo *et al*., 2021; Petersen *et al*., 2020). The most frequently prescribed NSAID is celecoxib due to its selective cyclooxygenase-2 (COX-2) inhibition, providing anti-inflammatory, analgesic and antipyretic effects with a lesser risk of gastrointestinal injury compared to non-selective NSAIDs (Tai and McAlindon, 2021; Sohail *et al.,* 2023). It is typically prescribed for osteoarthritis, rheumatoid arthritis and primary dysmenorrhea.

However, its overuse or prolonged use can still result in severe adverse effects like UGIB (Kang *et al.,* 2020). Celecoxib reduces gastric mucus secretion and impairs the mucosal barrier, predisposing the stomach and duodenum to acid- and pepsin-induced damage, resulting in gastritis, gastric ulcers, or duodenal ulcers and eventually bleeding (Kurlander *et al.,* 2022). As the long-term use of celecoxib grows, the early recognition of patients at high risk of UGIB is important in order to institute preventive measures, monitoring and early therapeutic changes, with the potential to decrease hospitalization and enhance patient outcomes (Ebadi, 2025a).

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Endoscopy remains the gold standard in UGIB diagnosis because of its high sensitivity and specificity. However, it is invasive, resource-intensive and operator-dependent and may even potentially worsen timely intervention in patients with active bleeding. Procedural risk and discomfort also limit its use in certain high-risk populations. Therefore, there is an urgent need for simple, inexpensive and stable predictive biomarkers that can aid in early risk stratification and guide decision-making before invasive procedures are performed (Yahya *et al.,* 2022).

Red cell distribution width (RDW) is a component of the complete blood count that is easily accessible and reflects red blood cell volume heterogeneity. Although traditionally used in anemia classification and follow-up, more recent studies link elevated RDW to systemic inflammation, cardiovascular disease and poor clinical outcomes in numerous conditions (Sim *et al.,* 2022; Chen *et al.,* 2024). Despite its promise, no study has evaluated RDW for the prediction of celecoxib-related UGIB.

This study was undertaken to confirm the hypothesis that elevated RDW is independently linked with celecoxib-related UGIB. Demonstrating its predictive value, RDW could provide a readily available, non-invasive and low-cost tool for the early clinical prophylaxis, risk assessment of patients and timely therapeutic measures.

MATERIALS AND METHODS

General Information

400 celecoxib-treated patients in our department from January 2018 to August 2024 were retrospectively enrolled. Of them, 379 patients had no upper gastrointestinal bleeding (non-UGIB group) and 21 patients had UGIB (UGIB group). The UGIB group was further categorized by bleeding volume: <250 mL (n = 8), 250-400 mL (n = 7) and >400 mL (n = 6).

Sample size was dictated by the number of eligible patients who met both inclusion and exclusion criteria over the study period. Although the UGIB subgroup was small, a post-hoc power calculation revealed the sample had 80% power to detect moderate effect sizes. Baseline information like gender, age, body mass index (BMI), alcohol consumption and smoking status was comparable in the groups ($P > 0.05$) (Table 1).

Inclusion and exclusion criteria

The inclusion criteria for the study were: patients with a clinical indication for treatment with celecoxib, aged 18 years and older and with normal cardiac, hepatic and renal function. The exclusion criteria were patients with hypersensitivity or allergic reaction to celecoxib, UGIB due to causes other than celecoxib, known hematologic disease, chronic anemia, coagulation disorder, or active bleeding from non-upper gastrointestinal sources. Individuals with autoimmune diseases or those who had undergone major surgery within a recent period were excluded. Patients with nutritional deficiencies, chronic inflammatory conditions, or concomitant medications with known influences on RDW were excluded to minimize confounding influences.

Diagnosis of UGIB

UGIB was diagnosed based on combined assessment of history, clinical presentation, laboratory findings and imaging studies (Karki *et al.,* 2022):

• **Medical history**: Detailed inquiry about past gastrointestinal disease such as gastric or duodenal ulcers, gastritis, or esophagitis (Ebadi, 2025b).

• **Clinical symptoms**: Melena, hematemesis, pallor, weakness, dizziness, or fever.

• **Laboratory tests**: Hemoglobin (Hb), red blood cell count (RBC) and hematocrit (HCT) were monitored, with the levels typically dropping within 3–4 hours after acute bleeding.

• **Imaging studies**: Gastroscopy, CT scans, selective angiography, or other imaging modalities were used to confirm diagnosis and identify bleeding sites.

UGIB severity evaluation

The degree of bleeding was graded based on objective clinical criteria (Ayonrinde *et al.,* 2022). A positive fecal occult blood test with melena was indicative of blood loss of more than 50 mL, hematemesis without systemic symptoms was equal to a blood loss of 250-400 mL and acute peripheral circulatory failure was indicative of blood loss of more than 1000 mL. Based on these criteria, the patients were divided into three groups according to the severity of bleeding: mild bleeding (<250 mL, n = 8), moderate bleeding (250-400 mL, n = 7) and severe bleeding (>400 mL, n = 6).

RDW and routine blood examination

Venous blood (5 mL) of fasting was obtained from all patients in the morning. RDW, Hb, RBC and HCT were analyzed using an automated hematology analyzer (Mindray BC-5000 Vet, reference RDW range 11.5–15.0%), which was regularly calibrated according to manufacturer guidelines.

Observation indicators

The primary observation parameters included comparison of RDW, Hb, RBC and HCT levels between non-UGIB and UGIB groups and also between UGIB subgroups of varying bleeding severities. Correlation tests were also performed to study the correlation of RDW with Hb, RBC and HCT. The predictive utility of RDW in the presence of celecoxib-induced UGIB was also compared using ROC curve analysis.

Statistical analysis

Data were analyzed using SPSS version 18.0. The continuous variables were shown as mean ± standard deviation ($\overline{x} \pm s$) and compared by independent-sample t-test, while categorical variables were shown as n (%) and compared by χ^2 test. Comparison among multiple groups was conducted by one-way ANOVA (F-test). Pearson correlation analysis was conducted to evaluate the correlation of RDW with other hematologic variables. Receiver operating characteristic (ROC) curves were drawn to establish the predictiveness of RDW and the area under the curve (AUC) and 95% confidence intervals (CIs) were reported. Missing data were managed by case-wise deletion and a P-value of <0.05 was considered statistically significant.

RESULTS

Comparison of RDW, Hb, RBC and HCT between non-UGIB and UGIB Groups

The UGIB group had significantly higher RDW values and significantly reduced Hb, RBC and HCT values compared to the non-UGIB group (all $P < 0.05$). These findings indicate extreme hematologic changes in celecoxib-induced UGIB patients. Median difference between groups for RDW was 5.97% (95% CI: 4.92–7.02), confirming a strong correlation with UGIB. For additional results in detail, refer to Table 2.

Comparison among UGIB subgroups based on bleeding severity

In patients with UGIB, RDW increasingly increased with worsening severity of bleeding volume, while Hb, RBC and HCT decreased in a stepwise manner. These patients also had significantly higher RDW and lower Hb, RBC and HCT values than both the <250 mL and 250–400 mL groups ($P < 0.05$). Likewise, the 250–400 mL group had worse hematologic parameters than the <250 mL group ($P < 0.05$). These findings demonstrate a strong correlation of RDW with the extent of blood loss and RDW is revealed as an independent predictor of the severity of bleeding (Table 3).

Correlation between RDW and hematologic indices

Pearson correlation analysis identified negative correlations between RDW and Hb ($r = -0.543$), RBC ($r = -0.525$) and HCT ($r = -0.509$) (all $P < 0.001$), suggesting that increased RDW is associated with worsening anemia and reduction in hematocrit (Table 4).

Predictive value of RDW for celecoxib-induced UGIB

ROC curve analysis identified the onset cutoff for RDW of 16.32% with 83.92% sensitivity and 60.35% specificity to predict celecoxib-induced UGIB. The area under the curve (AUC) was 0.773 (95% CI: 0.709-0.959, $P < 0.001$), with good discriminative performance (Table 5, Fig. 1). The respective Youden Index was 0.455, attesting to clinical utility of RDW as a non-invasive biomarker for early risk stratification. RDW ≥16.32% patients are significantly more likely to develop UGIB, attesting to its preventive monitoring and clinical decision-making utility.

RDW was far greater in celecoxib-induced UGIB patients compared to non-bleeding controls, indicating its good correlation with the complication. In addition, RDW values increased proportionally with worsening bleeding, showing that RDW might correlate with the amount of blood loss. There was very high negative correlation between RDW and Hb, RBC and HCT, which means that rising RDW values are related to worsening anemia and hematocrit reduction. ROC curve analysis also confirmed RDW as an acceptable and non-invasive marker for predicting celecoxib-induced UGIB, confirming its future utility as an early risk stratification biomarker and clinical management.

DISCUSSION

Celecoxib is a selective COX-2 inhibitor that is widely prescribed in managing pain and inflammation due to its favorable gastrointestinal safety over traditional NSAIDs. However, celecoxib can still cause upper gastrointestinal bleeding (UGIB) in patients with predisposing conditions such as peptic ulcer disease or concurrent drug usage (Carvajal-Gutiérrez *et al.,* 2024; Durak *et al.,* 2023). Melena, hematemesis, azotemia and hemorrhagic shock and multi-organ failure in severe cases are signs and symptoms of UGIB (Hao *et al*., 2022). While the majority of UGIB events are self-limiting, the patients with advanced cases may require endoscopic intervention, transfusion, or surgery and untreated UGIB may be fatal (Mbambo *et al.,* 2020).

Endoscopy is the gold standard for the diagnosis of UGIB because direct visualization of the bleeding site is possible. It is invasive, though time-consuming and operator-dependent, thereby potentially leading to delayed diagnosis or lack of consistency in interpretation (Vimonsuntirungsri *et al.,* 2024). These are the limitations in favor of the requirement for simple, non-invasive and reproducible prediction markers to facilitate early risk stratification and timely intervention. RDW is a routinely available hematological parameter reflecting red blood cell size variation. Previously used to evaluate anemia, RDW has recently been associated with systemic inflammation, cardiovascular disease and adverse outcomes in severe illnesses (Sim *et al.,* 2022; Chen *et al.,* 2024). However, its future predictive ability for celecoxib-induced UGIB was not evaluated prior to this research.

In the current study, RDW was significantly higher in celecoxib-induced UGIB patients compared with non-bleeding patients. Furthermore, RDW increased alongside increasing bleeding severity, while Hb, RBC and HCT decreased. ROC curve analysis indicated that RDW ≥16.32% could predict UGIB with 83.92% sensitivity and 60.35% specificity (AUC = 0.773, 95% CI: 0.709-0.959).

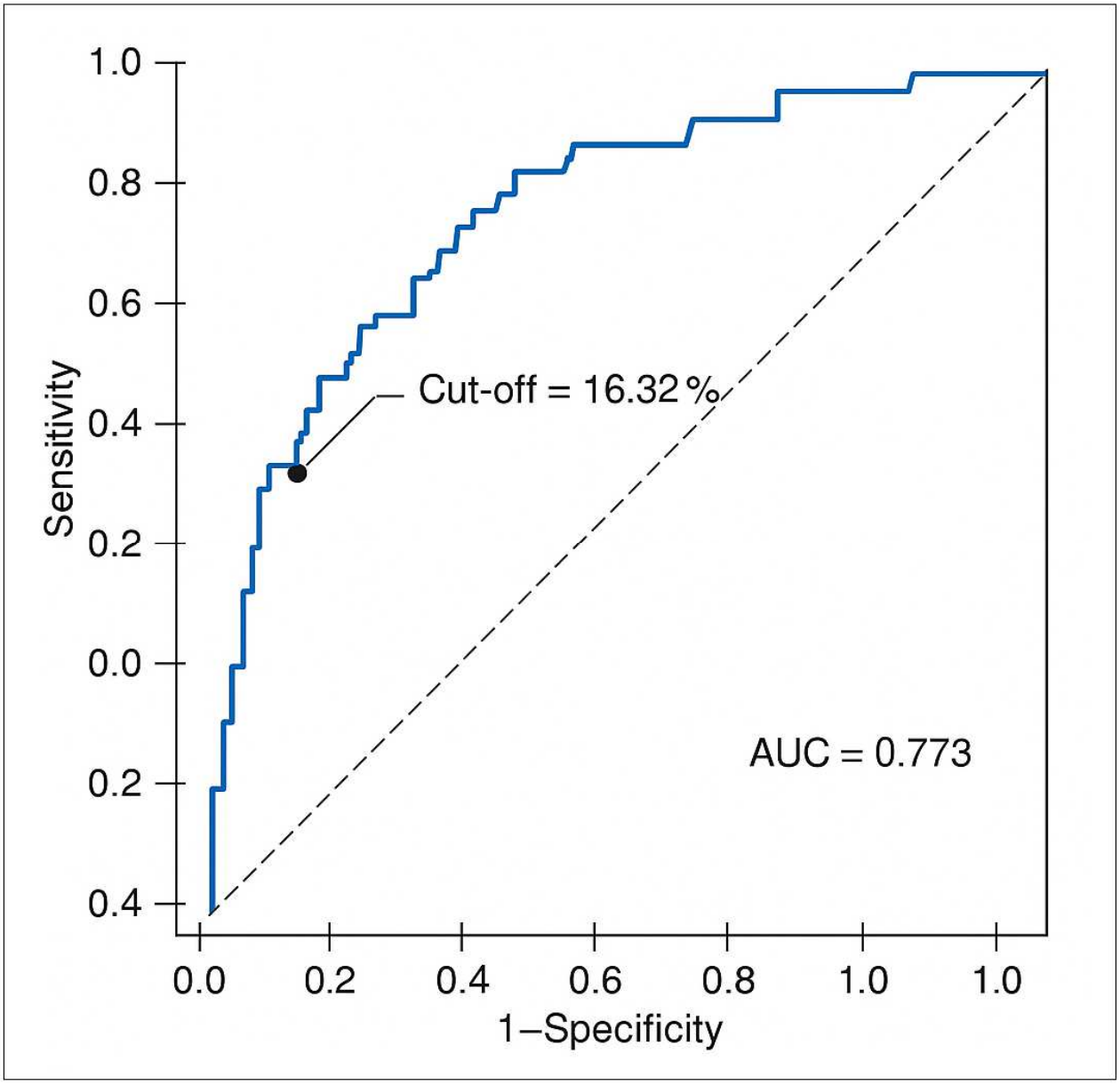

Fig. 1. ROC curve showing the predictive value of RDW for celecoxib-induced UGIB; the curve demonstrates the best cut-off of 16.32%, indicating excellent diagnostic accuracy

Table 1: Comparison of general data between groups

General information	Non-UGIB group (n=379)	UGIB group (n=21)	t/χ^2 value	P value
Gender [n (%)]				
Male	204 (53.83)	11 (52.38)	0.023	0.887
Female	175 (46.17)	10 (47.62)		
Age (years)	50.69 ± 11.68	49.97 ± 10.29	0.372	0.708
BMI (kg/m²)	24.20 ± 1.82	24.00 ± 1.97	0.459	0.639
Smoking History [n (%)]			0.473	0.492
Yes	160 (42.22)	8 (38.10)		
No	219 (57.78)	13 (61.90)		
Alcohol Consumption [n (%)]			0.454	0.501
Yes	326 (86.02)	18 (85.71)		
No	53 (13.98)	3 (14.29)		

Table 2: Comparison of RDW, Hb, RBC and HCT between Groups (mean ± SD)

Indicator	Non-UGIB group (n = 379)	UGIB group (n = 21)	t value	P value
RDW (%)	12.93 ± 2.08	18.90 ± 3.25	9.011	0.000
Hb (g/L)	149.53 ± 7.76	89.06 ± 6.33	17.383	0.000
RBC ($\times 10^{12}$/L)	5.11 ± 0.36	4.36 ± 0.47	4.376	0.036
HCT (%)	46.50 ± 5.63	38.77 ± 5.83	8.714	0.000

Table 3: RDW, Hb, RBC and HCT in UGIB subgroups (mean ± SD)

Indicator	Bleeding <250 mL (n = 8)	Bleeding 250–400 mL (n = 7)	Bleeding >400 mL (n = 6)
RDW (%)	16.14 ± 2.65	18.45 ± 3.42*	22.57 ± 4.32*#
Hb (g/L)	141.85 ± 5.84	85.78 ± 7.96*	57.16 ± 6.23*#
RBC ($\times 10^{12}$/L)	4.88 ± 0.54	4.10 ± 0.47*	3.47 ± 0.53*#
HCT (%)	42.37 ± 6.11	38.09 ± 7.06*	32.45 ± 5.69*#

Table 4: RDW correlation with Hb, RBC and HCT

Indicator	Hb	RBC	HCT
RDW	r = -0.543	r = -0.525	r = -0.509
P Value	0.000	0.000	0.000

Table 5: Predictive value of RDW for celecoxib-induced UGIB

Parameter	Value
RDW cutoff (%)	16.32
Sensitivity (%)	83.92
Specificity (%)	60.35
AUC	0.773
95% CI	0.709-0.959
Youden index	0.455

The results support RDW as a simple biomarker for predicting at-risk patients prior to clinical deterioration. The resulting relationship between RDW and UGIB is biologically plausible. Blood loss provokes erythropoietin release, which provokes the release of immature red cells of variable sizes, increasing RDW. Inflammatory cytokines such as IL-1, IL-6 and TNF-α, occurring in elevated concentrations with mucosal injury, suppress erythropoiesis and red cell maturation, contributing to anisocytosis (Nakamura *et al.,* 2024).

Furthermore, celecoxib-mediated mucosal damage may also disturb nutrient absorption, exacerbating iron deficiency and RDW variability. Thus, elevated RDW signals both bleeding severity and systemic inflammatory reaction, linking it with poor prognosis. These findings are supported by recent studies that RDW is a predictor of severity and outcome of gastrointestinal bleeding. For instance, Lee *et al*. (2023) demonstrated that increased RDW was predictive of mortality in patients with acute GI hemorrhage and Meram *et al.* (2024) reported its use in the risk stratification of NSAID-induced gastric complications. The current study builds upon this work by considering celecoxib-treated patients exclusively, a group for whom predictive factors are of utmost importance. RDW is inexpensive, rapid and easily obtained through routine complete blood count. Incorporating RDW into risk-assessment models could allow clinicians to identify high-risk celecoxib users and urge intensified monitoring, drug adjustment, or early diagnostic evaluation. This approach could reduce inappropriate endoscopies, improve patient safety and optimize resource utilization in clinical practice (Rader *et al.,* 2017).

The current study has a few limitations. Firstly, the UGIB group was limited in number (n = 21), which lowers the statistical power and potentially increases the risk of type II errors. Secondly, RDW may be affected by secondary conditions such as anemia, nutritional deficiency, chronic inflammatory diseases, or comorbidities, not entirely excluded despite exclusion criteria. Third, retrospective single-center design is limited by generalizability. Larger cohorts prospective, multicenter trials are warranted to validate these initial findings and establish standardized RDW thresholds for clinical usage.

CONCLUSION

RDW is markedly elevated in celecoxib-treated patients who experience UGIB and possesses robust predictive value. As a non-invasive, low-cost, readily accessible test, RDW may serve as an early warning biomarker for

clinicians to identify at-risk patients and take prevention measures. The incorporation of RDW in routine monitoring has the potential to reduce reliance on invasive testing such as endoscopy, enhance patient safety and assist with therapeutic decision-making. In the future, large-scale multicenter trials are needed to confirm these observations and include RDW in daily clinical risk stratification algorithms.

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Author's contributions
Wang Huazi: Conceptualization, methodology, data curation, analysis, writing—original draft, writing—review and editing, supervision. The author was responsible for the design of the study, data collection, statistical analysis, and manuscript preparation.

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Data availability statement
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval
This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Xincang Town Central Health Center (Pinghu City, Zhejiang Province) of China (Approval No. 2024-ETH-015). Given the retrospective design, the requirement for written informed consent was waived. Patient data were anonymized and handled with strict confidentiality to protect privacy.

Conflict of interest
The authors declare that they have no conflicts of interest relevant to this study.

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