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NON-SELECTIVE BETA-BLOCKERS WITH OR WITHOUT ENDOSCOPIC BAND LIGATION IN PORTO-SINUSOIDAL VASCULAR DISEASE: A PHENOTYPE-DRIVEN APPROACH

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ABSTRACT

Background and Aims: Porto-sinusoidal vascular disease (PSVD) is a cause of non-cirrhotic portal hypertension frequently complicated by variceal bleeding. In the absence of disease-specific evidence, management strategies are largely extrapolated from cirrhosis, although their applicability to PSVD remains uncertain. This study aimed to evaluate real-world therapeutic strategies and identify factors guiding treatment decisions and bleeding risk in PSVD.

Methods: We conducted a retrospective single-center study including patients with PSVD followed between January 2018 and December 2025. Patients with less than two years of follow-up or incomplete data were excluded. Clinical, endoscopic, and therapeutic variables were analyzed, with a focus on non-selective beta-blockers (NSBB), endoscopic band ligation (EBL), and hemorrhagic decompensation. Univariate and multivariate analyses were performed to identify predictors of bleeding and determinants of combined therapy.

Results: A total of 42 patients were included (mean age 38.8 ± 14.4 years, 73.8% female). Portal hypertension was nearly universal, with esophageal varices in 90.5%, gastric varices in 31.0%, and portal hypertensive gastropathy in 35.7%. Prothrombotic conditions predominated, and splanchnic thrombosis was present in 61.9% of patients.

NSBB therapy could not be initiated in 23.8% of patients. EBL was performed in 66.7%, mainly for secondary prophylaxis or NSBB intolerance. Patients receiving combined NSBB+EBL therapy exhibited a more severe phenotype, with higher rates of esophageal varices (100% vs 69.2%, p = 0.007) and hemorrhagic decompensation (60.7% vs 14.3%, p = 0.007).

Gastric varices (p = 0.008) and portal hypertensive gastropathy (p = 0.047) were significantly associated with bleeding. Prothrombotic etiology was not associated with hemorrhagic risk (p = 1.000). Multivariate analysis did not identify independent predictors of EBL requirement.

Conclusions: In PSVD, management of variceal bleeding appears to be driven by the severity of portal hypertension and endoscopic phenotype rather than by the underlying prothrombotic condition. These findings support a phenotype-driven approach and highlight the limitations of extrapolating cirrhosis-based strategies to this heterogeneous disease.

KEYWORDS

Porto-sinusoidal vascular disease, Non-cirrhotic portal hypertension, Esophageal varices, Non-selective beta-blockers, Endoscopic band ligation, Hemorrhagic decompensation, Portal hypertension, Anticoagulation

MAIN ARTICLE

INTRODUCTION

Porto-sinusoidal vascular disease represents a spectrum of hepatic vascular disorders characterized by non-cirrhotic portal hypertension, with esophageal varices being a significant complication that predisposes patients to life-threatening hemorrhage [1]. The prophylactic management of variceal bleeding traditionally involves strategies aimed at reducing portal pressure, including pharmacological interventions such as non-selective beta-blockers and endoscopic variceal ligation [2, 3].

According to the Baveno VII Consensus Workshop, non-selective beta-blockers (NSBB) are recommended as first-line therapy for primary and secondary prophylaxis of variceal bleeding, while endoscopic band ligation (EBL) is reserved for high-risk varices or in cases of NSBB intolerance [4]. However, these recommendations are not specific to PSVD. This gap underscores the need for PSVD-specific evidence to guide variceal management in this population.

In clinical practice, patients with PSVD often exhibit heterogeneous presentations, including varying degrees of portal hypertension, presence of splanchnic thrombosis, and different prothrombotic profiles. These factors may influence therapeutic decisions beyond current guideline recommendations. Furthermore, evidence indicates that the rate of progression to varices at risk of bleeding and the incidence of first variceal hemorrhage are significantly higher in patients with non-cirrhotic portal hypertension, including PSVD, compared to those with compensated cirrhosis [5], potentially warranting more frequent endoscopic surveillance intervals and customized prophylactic approaches despite the lack of specific guidelines [4].

The aim of this study was, therefore, to evaluate real-world management strategies in patients with PSVD by comparing NSBB monotherapy versus combination therapy with NSBB and EBL, and to identify clinical, endoscopic, and etiological factors influencing treatment choice and bleeding risk.

METHODS

Study design and population

This was a retrospective, single-center study conducted at a tertiary referral center. All patients diagnosed with PSVD between January 2018 and December 2025 were screened.

Inclusion and exclusion criteria

Patients were included if they had a confirmed diagnosis of PSVD and at least 2 years of follow-up. Patients whose diagnosis was revised during follow-up and those with incomplete clinical or endoscopic data were excluded.

Data collection

The following variables were collected: demographics; etiology (prothrombotic disorders); presence of splanchnic thrombosis; anticoagulation therapy; endoscopic findings (esophageal varices [EV], gastric varices [GV] and portal hypertensive gastropathy [PHG]); treatment modalities (NSBB, EBL); and occurrence of hemorrhagic decompensation.

Outcomes

The primary outcome was hemorrhagic decompensation. The secondary outcome was the identification of determinants of combined therapy (NSBB+EBL).

Statistical analysis

Univariate analysis was performed using the Chi-square test or Fisher's exact test, as appropriate. Multivariate logistic regression was then performed. A p-value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

A total of 42 patients were included, with a mean age of 38.8 ± 14.4 years, and a marked female predominance (73.8%).

Portal hypertension was nearly universal at baseline. Esophageal varices were present in 90.5% of patients, gastric varices in 31.0%, and portal hypertensive gastropathy (PHG) in 35.7%, reflecting a globally advanced portal hypertensive phenotype within the cohort (Figure 1).

The etiological profile was predominantly prothrombotic. Protein C deficiency was identified in 38.1% of patients, combined protein C and S deficiency in 33.3%, and isolated protein S deficiency in 11.9%. Portal or splanchnic thrombosis was documented in 61.9% of cases. Long-term anticoagulation was administered in 76.2% of patients, mainly using direct oral anticoagulants (DOACs). The underlying condition was considered controlled in 54.8% of cases.

Therapeutic strategies

Non-selective beta-blockers (NSBB) were considered for all patients; however, initiation was not feasible in 10 patients (23.8%) due to contraindications or anticipated hemodynamic intolerance.

Endoscopic band ligation (EBL) was performed in 28 patients (66.7%), primarily for secondary prophylaxis or as an alternative in patients unsuitable for NSBB therapy (Figure 2).

Patients receiving combined NSBB+EBL therapy exhibited a significantly more severe portal hypertensive phenotype compared to those treated with NSBB alone. In particular, esophageal varices were present in all patients in the combined therapy group (100%) versus 69.2% in the NSBB-only group ($p = 0.007$) (Figure 3). Similarly, the rate of hemorrhagic decompensation was markedly higher in the combined therapy group (60.7% vs 14.3%, $p = 0.007$) (Figure 4).

Predictors of hemorrhagic decompensation

Univariate analysis identified gastric varices ($p = 0.008$) and portal hypertensive gastropathy ($p = 0.047$) as significant predictors of hemorrhagic decompensation (Table 1).

A trend toward increased bleeding risk was observed in patients without anticoagulation ($p = 0.055$) and in those with uncontrolled underlying disease ($p = 0.061$), although these associations did not reach statistical significance.

In contrast, the specific prothrombotic etiology, including protein C and/or S deficiency, was not associated with hemorrhagic risk ($p = 1.000$).

Multivariate analysis

Multivariate analysis did not identify anticoagulation status, disease control, or type of protein deficiency as independent predictors of the need for EBL. These findings suggest that

therapeutic escalation is primarily driven by the severity of portal hypertension rather than by the underlying etiological profile.

DISCUSSION

Principal findings

This study highlights the challenges in managing variceal bleeding in patients with porto-sinusoidal vascular disease, particularly emphasizing the absence of PSVD-specific guidelines and the current reliance on strategies extrapolated from cirrhotic cohorts.

PSVD, recognized as a heterogeneous disorder characterized by non-cirrhotic portal hypertension with diverse underlying etiologies including prothrombotic states, immunological conditions, and drug exposures [6–8], was managed in this cohort through strategies prioritizing the endoscopic severity of portal hypertension over etiological factors. In this cohort of PSVD patients, therapeutic decision-making for variceal bleeding prevention appeared to be primarily driven by the severity of portal hypertension and endoscopic phenotype rather than by the underlying prothrombotic condition, consistent with the absence of PSVD-specific guidelines and the observed higher rates of advanced variceal features and hemorrhagic decompensation prompting combined NSBB+EBL therapy [4].

Severity-driven management

This approach reflects a pragmatic adaptation of variceal bleeding prophylaxis paradigms traditionally applied to cirrhotic patients, where endoscopic risk stratification dictates the intensity of intervention, particularly for patients with large varices or those demonstrating clinical signs of high bleeding risk [9]. Specifically, the presence of gastric varices and portal hypertensive gastropathy were identified as significant predictors of hemorrhagic decompensation, necessitating a more aggressive therapeutic approach [10].

Notably, the higher incidence of hemorrhagic decompensation among patients selected for combined NSBB+EBL therapy underscores that therapeutic escalation identifies those with advanced endoscopic stigmata (e.g., universal esophageal varices), yet does not demonstrate additive efficacy beyond NSBB monotherapy. This is consistent with meta-analyses showing no reduction in bleeding risk with combination therapy versus NSBB alone in primary prophylaxis [11, 12].

Comparison with guidelines

The Baveno VII consensus positions non-selective beta-blockers as first-line therapy for primary prophylaxis in cirrhosis, with combination therapy recommended for secondary prophylaxis [4]. These guidelines extrapolate cirrhosis-based algorithms to PSVD due to insufficient disease-specific data [4]; however, the distinct pathophysiology of PSVD [7, 8] renders such approaches potentially inadequate; our findings suggest that extrapolation of cirrhotic algorithms to PSVD may be insufficient to capture the heterogeneity of clinical presentation. Given the higher incidence of variceal bleeding and faster progression of varices in patients with non-cirrhotic portal hypertension, a more frequent endoscopic follow-up may be warranted, differing from guidelines established for cirrhotic populations [13]. However, the applicability of non-selective beta-blockers in primary prophylaxis for PSVD remains contentious, given conflicting evidence regarding their efficacy in preventing initial variceal hemorrhage in non-cirrhotic portal hypertension, where their benefit may not consistently outweigh potential adverse effects [14, 15].

Role of endoscopic phenotype

Endoscopic features, particularly gastric varices and portal hypertensive gastropathy—which univariate analysis identified as strong and significant predictors of hemorrhagic decompensation, respectively—emerged as key markers of clinically significant portal hypertension and bleeding risk, likely reflecting higher portal pressure gradients and distinct vascular architecture characteristic of PSVD [16–18]. This suggests that targeted interventions based on these endoscopic markers, rather than solely on underlying prothrombotic states, may be more efficacious in guiding therapeutic decisions and preventing adverse outcomes in PSVD patients.

Prothrombotic disorders

While prothrombotic disorders, including protein C and/or S deficiency, are central to the pathogenesis of PSVD [6–8, 19], they do not appear to determine the clinical severity of portal hypertension, as neither the specific prothrombotic etiology nor anticoagulation status emerged as predictors of hemorrhagic decompensation or the need for endoscopic band ligation in univariate or multivariate analyses. This observation underscores that while thrombophilic states initiate the disease, the subsequent hemodynamic alterations and their endoscopic manifestations are the primary determinants of clinical management and bleeding risk [20]. This dissociation between thrombotic predisposition and the clinical course of portal

hypertension highlights the need for a comprehensive assessment that integrates hemodynamic and endoscopic findings with etiological considerations to optimize patient management [21].

Anticoagulation

Although not statistically significant ($p = 0.055$), anticoagulation demonstrated a trend toward lower rates of hemorrhagic decompensation in this cohort, suggesting a potential protective role through prevention of thrombotic progression and stabilization of portal hypertension. This observation merits further investigation and is consistent with reports of a favorable safety profile and survival benefit of anticoagulation in non-cirrhotic portal hypertension without increased bleeding risk [10, 13, 22]. This protective effect may be attributed to improved portal venous patency and reduction in portal vein thrombosis propagation, thereby mitigating the severity of portal hypertension and its related complications [23].

Clinical implications

These findings support a phenotype-driven approach to management, emphasizing the central role of endoscopic assessment in risk stratification and therapeutic decision-making rather than relying solely on prothrombotic etiology [4, 13, 24]. While screening for underlying thrombophilia is essential for etiological diagnosis, it appears to have limited utility in predicting the severity of portal hypertension or guiding immediate variceal management strategies in PSVD [4, 13, 19].

Limitations

This study has several limitations. Its retrospective design may have introduced selection and information biases. Conducted at a single tertiary center, it may limit the generalizability of the findings. The relatively small sample size reduced statistical power and potentially limited identification of independent predictors. Moreover, treatment allocation was not randomized; patients receiving combined NSBB and endoscopic band ligation likely represented a subgroup with more severe portal hypertensive disease, introducing indication bias.

Despite these limitations, our study provides valuable real-world insights into managing porto-sinusoidal vascular disease, a rare, underexplored condition for which evidence-based recommendations remain limited.

CONCLUSION

In patients with porto-sinusoidal vascular disease, strategies for the prevention of variceal bleeding appear to be primarily driven by the severity of portal hypertension and endoscopic phenotype rather than by the underlying prothrombotic etiology. In particular, gastric varices and portal hypertensive gastropathy emerged as key markers of hemorrhagic risk.

These findings support a phenotype-driven approach to management, emphasizing the central role of endoscopic assessment in therapeutic decision-making. Further prospective studies are needed to better define disease-specific strategies and to validate tailored approaches in this heterogeneous population.

FIGURES

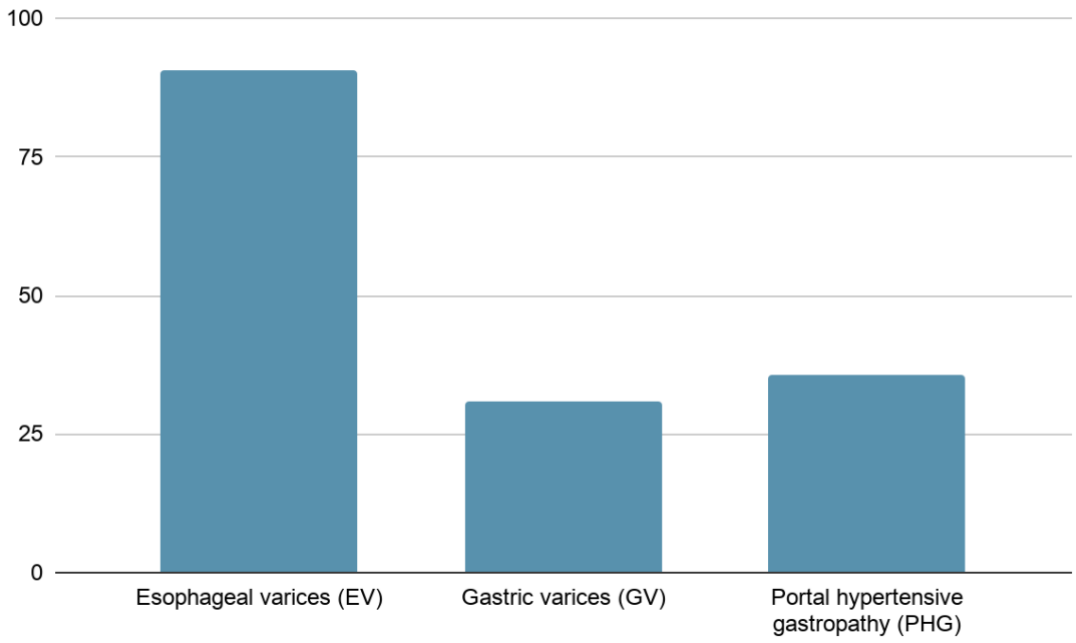


Figure 1: Baseline portal hypertensive features in patients with porto-sinusoidal vascular disease

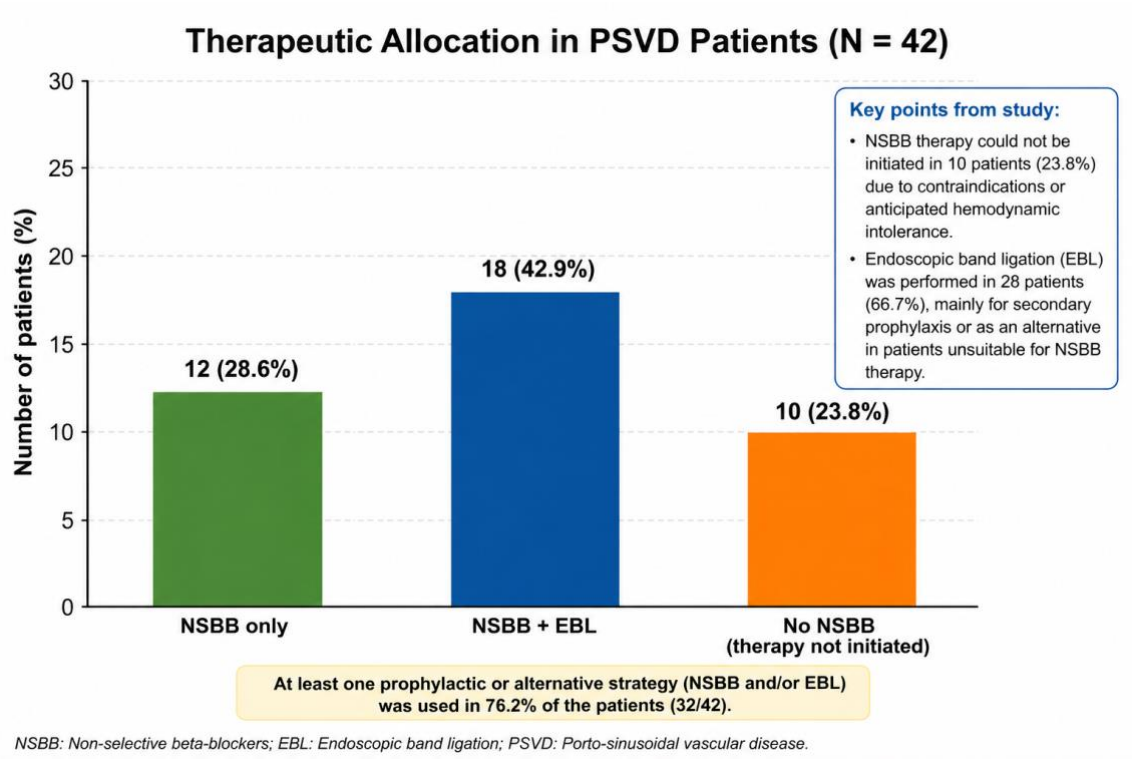


Figure 2: Therapeutic allocation in patients with porto-sinusoidal vascular disease

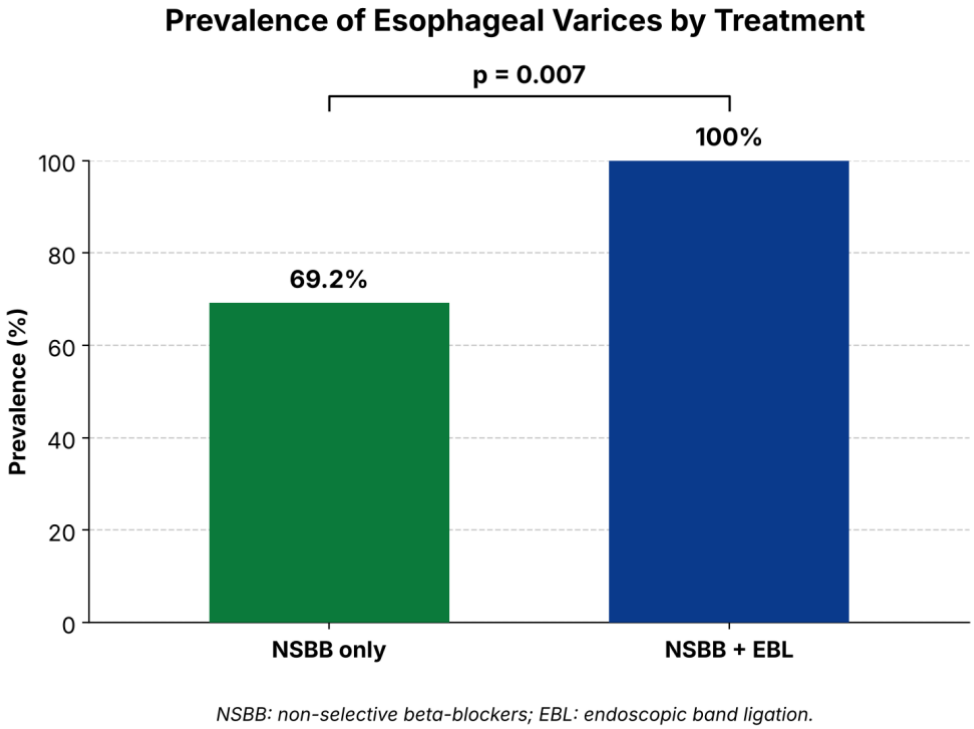


Figure 3: Prevalence of Esophageal Varices According to Treatment Strategy

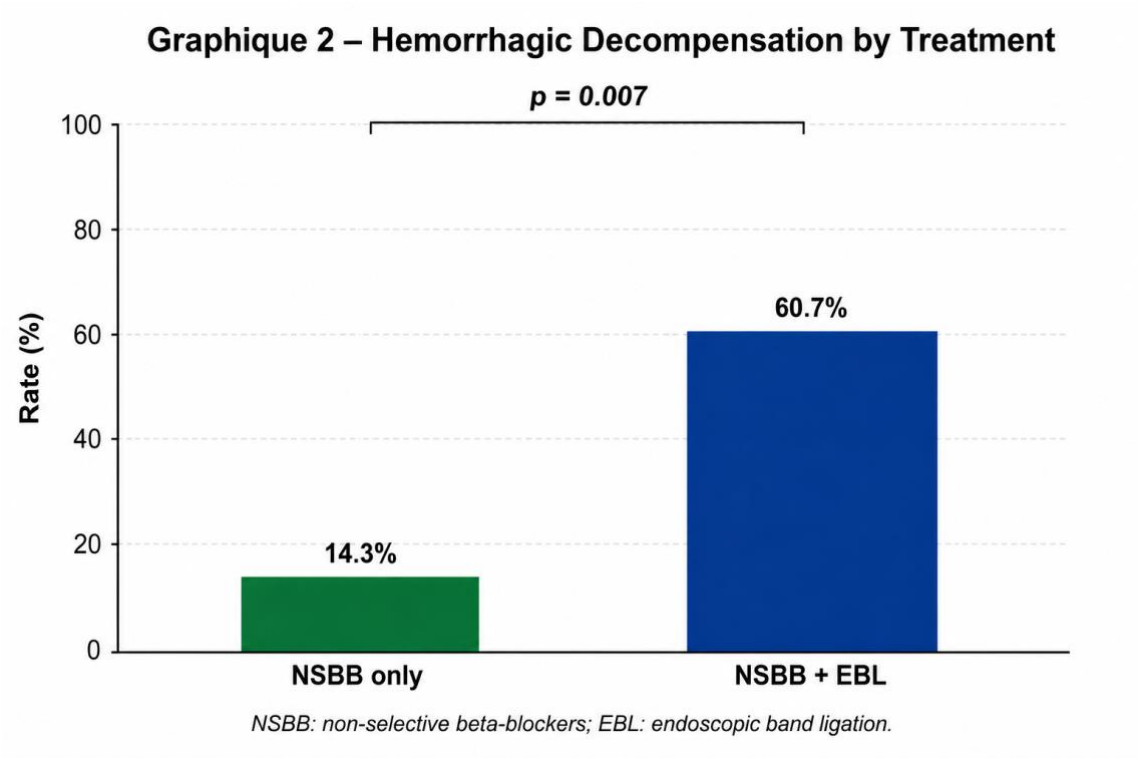


Figure 4: Rate of Hemorrhagic Decompensation by Treatment Group

TABLES

Table 1: Univariate analysis of factors associated with hemorrhagic decompensation in patients with porto-sinusoidal vascular disease

Variable	p-value
Gastric varices	0.008
Portal hypertensive gastropathy (PHG)	0.047
Absence of anticoagulation	0.055
Uncontrolled underlying disease	0.061
Protein C and/or S deficiency	1.000

p-values were obtained by univariate analysis (Chi-square or Fisher's exact test). PHG: portal hypertensive gastropathy.

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Conflicts of interest: The authors declare no conflicts of interest.

Ethics approval: This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki. Given its retrospective design and the use of fully anonymized data, it was exempted from formal ethics committee approval.

Informed consent: The requirement for informed consent was waived owing to the retrospective nature of the study and the anonymization of all patient data.

Author contributions: All authors approved the final version.

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