Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Comorbidity Burden and Early Postoperative Rebleeding After Supratentorial Intracerebral Hematoma Evacuation: A Retrospective Cohort Study

Jan Banoci
Pavol Jozef Šafárik University
Veronika Banoci Magocova
veronika.magocova@upjs.sk

Pavol Jozef Šafárik University
Vladimir Katuch
Pavol Jozef Šafárik University
Kamil Knorovsky
Pavol Jozef Šafárik University
Michaela Skovranova
Pavol Jozef Šafárik University

Research Article

Keywords: intracerebral hemorrhage, hematoma evacuation, postoperative rebleeding, comorbidity burden, multimorbidity

Posted Date: March 10th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-8926209/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Early postoperative rebleeding after intracerebral hemorrhage (ICH) evacuation remains a highly consequential complication, associated with neurological deterioration and potential need for reintervention. Systemic patient factors—particularly multimorbidity, chronic alcohol use (often accompanied by liver disease), renal dysfunction, and anticoagulant therapy—may modify early bleeding risk.

Aim

To evaluate the association between comorbidity burden (0–1 vs multimorbidity ≥ 2 chronic conditions) and early postoperative rebleeding after ICH evacuation, and to discuss plausible mechanisms and clinical implications related to alcohol-related disease, hepatopathy, nephropathy, and anticoagulation.

Methods

Retrospective cohort analysis of 111 patients undergoing surgery for supratentorial ICH with the explicit goal of hematoma evacuation (conventional craniotomy, n = 76; endoscopic-assisted procedures, n = 35). Routine postoperative CT was performed within 6 hours and at 24 hours. Early rebleeding was assessed within 24 hours and defined as a new hyperdense component within the evacuated hematoma cavity and/or pericavitary surrounding brain after gross-total evacuation had been achieved or confirmed on early postoperative CT. Comorbidity burden was classified as 0–1 comorbidity versus multimorbidity (≥ 2 chronic conditions).

Results

Overall, 11/111 (9.9%) patients developed early postoperative rebleeding. Rebleeding rates did not differ significantly by surgical approach (7/76 [9.2%] conventional craniotomy vs 4/35 [11.4%] endoscopic-assisted; Fisher’s exact p = 0.739; OR 1.27, 95% CI 0.35–4.66). Comorbidity burden showed a strong association with rebleeding: 2/78 (2.6%) in the 0–1 comorbidity group versus 9/33 (27.3%) in the multimorbidity group (Fisher’s exact p = 0.00026), corresponding to an OR of 14.25 (95% CI 2.88–70.54) and a risk ratio of 10.64 for multimorbid versus low-burden patients.

Conclusion

Multimorbidity (≥ 2 chronic conditions) is a strong clinical marker of increased early postoperative rebleeding risk after ICH evacuation. These findings support intensified perioperative risk mitigation in

high-burden patients, including strict hemodynamic control, metabolic stabilization, correction of coagulopathy, alcohol-withdrawal prophylaxis when relevant, and individualized antithrombotic management.

Introduction

Despite advances in minimally invasive and conventional techniques for intracerebral hematoma evacuation, postoperative rebleeding remains a feared complication capable of negating surgical benefit. Early rebleeding may cause rapid neurological deterioration, increase perihematomal mass effect, and prompt emergent reoperation, thereby worsening functional outcomes and increasing mortality(1). While surgical technique and local hemostasis are critical, the pathophysiology of recurrent bleeding is multifactorial and frequently extends beyond operative factors; systemic conditions influence vascular fragility, perioperative hemodynamics, coagulation competence, and tissue repair capacity.

Common comorbidities such as hypertension, diabetes mellitus, obesity, and cardiovascular disease may increase postoperative bleeding risk through small-vessel disease, endothelial dysfunction, and perioperative blood pressure lability. Chronic alcohol use adds further vulnerability by promoting thrombocytopenia and qualitative platelet dysfunction, malnutrition, immune dysregulation, and alcohol-related liver disease with impaired synthesis of clotting factors. Renal dysfunction—particularly in advanced chronic kidney disease and dialysis-dependent patients—contributes via uremic platelet dysfunction, anemia, fluid shifts, and frequent exposure to anticoagulation during dialysis sessions. Finally, anticoagulant therapy (vitamin K antagonists and direct oral anticoagulants) remains a central driver of impaired perioperative hemostasis, necessitating structured reversal, laboratory assessment where applicable, and careful decisions regarding restart timing(2).

In clinical practice, however, these risk domains rarely occur in isolation. Patients presenting with supratentorial ICH often exhibit clusters of chronic conditions that jointly shape perioperative vulnerability. A count-based comorbidity burden provides a pragmatic way to operationalize this systemic risk phenotype, potentially enabling bedside stratification without relying on a single dominant diagnosis. Nevertheless, evidence quantifying the relationship between comorbidity burden and early postoperative rebleeding after ICH evacuation remains limited, and existing studies often focus on individual comorbidities or technique-related factors rather than the cumulative effect of multimorbidity(3).

Therefore, we aimed to evaluate the association between comorbidity burden—defined as 0–1 comorbidity versus multimorbidity (≥ 2 chronic conditions)—and early postoperative rebleeding within 24 hours after surgical evacuation of supratentorial ICH. In addition, we discuss plausible biological mechanisms and perioperative management implications related to alcohol-related disease, hepatopathy, nephropathy, and anticoagulant exposure, with the goal of informing risk mitigation strategies in high-burden patients(4).

Material and methods

This study was designed as a retrospective observational cohort study. We reviewed data of 142 consecutive patients who underwent neurosurgical treatment for supratentorial intracerebral hemorrhage (ICH) between January 2016 and December 2025 at the Department of Neurosurgery, University Hospital L. Pasteur (UNLP) and Pavol Jozef Šafárik University (UPJŠ), Košice, Slovakia (Fig. 1).

The study protocol was approved by the local Institutional Ethics Committee. The study was performed in accordance with applicable guidelines and regulations and in compliance with the Declaration of Helsinki. Given the retrospective design and use of anonymized data, informed consent for the use of clinical data was obtained when feasible; when not feasible, anonymized data were included in accordance with the ethics approval and institutional regulations.

Inclusion criteria

Patients were eligible for inclusion if they met all of the following criteria: (1) acute spontaneous supratentorial intracerebral hemorrhage (SSICH) confirmed on non-contrast CT, located in the subcortical (lobar), putaminal, or thalamic region, with or without intraventricular extension; (2) hematoma volume ≥ 30 mL on baseline CT; (3) Glasgow Coma Scale (GCS) score ≥ 5 at presentation (or immediately prior to surgery); (4) Surgical treatment performed within 72 hours of hospital admission.

Exclusion criteria

Patients were excluded if any of the following were present: (1) intracerebral hemorrhage secondary to an underlying structural lesion or non-spontaneous etiology, including arteriovenous malformation, intracranial aneurysm, tumor-related hemorrhage, or traumatic brain injury; (2) GCS score < 5; (3) irreversible or non-correctable coagulopathy at the time of surgical decision-making (e.g., persistent coagulation abnormalities despite standard reversal/correction measures, at the discretion of the treating team); (4) multiple intracranial hemorrhages (i.e., multifocal hemorrhagic lesions) on baseline imaging; (5) incomplete clinical or imaging data precluding reliable assessment of exposures and outcomes.

Exposure: comorbidity burden

Comorbidity burden was defined as the number of pre-existing chronic conditions documented at admission and/or during preoperative assessment and was used as the primary exposure reflecting systemic vulnerability. Patients were classified into two mutually exclusive categories: low burden (0–1 comorbidity) and multimorbidity (≥ 2 chronic conditions)(2).

A comorbidity was counted if it represented a chronic, clinically established diagnosis present before the index hemorrhage with plausible relevance to perioperative risk. Counted conditions included: arterial

hypertension, diabetes mellitus, obesity (BMI in the obese range or documented clinical diagnosis when BMI was unavailable), cardiovascular disease (coronary artery disease/prior myocardial infarction, chronic heart failure, peripheral arterial disease, atrial fibrillation), chronic liver disease (hepatopathy), chronic kidney disease (nephropathy) (dialysis dependence recorded where applicable), chronic alcohol use disorder (ethylism), and other chronic systemic illnesses consistently documented in the record(5).

Comorbidities were ascertained retrospectively from routine clinical documentation, including admission history, anesthesiology/preoperative assessment, internal medicine/neurology consultations, and discharge diagnoses when consistent with pre-existing disease; medication history was considered supportive only. Acute in-hospital complications were not counted. Each condition was counted once per patient, and redundant diagnoses describing the same disease entity were consolidated. Anticoagulant therapy was not included in the comorbidity count and was handled as a separate exposure domain, whereas the underlying indication (e.g., atrial fibrillation) was counted when present. Ethylism was counted when chronic harmful alcohol use was documented in the medical history (e.g., dependence or long-term harmful consumption). The binary split (0–1 vs ≥ 2) was chosen to provide clinically intuitive stratification and to avoid sparse categories given the number of outcome events.

Surgical management and perioperative imaging

On admission, all patients underwent non-contrast head CT and, when clinically indicated, CT angiography (CTA) in the emergency department to confirm the diagnosis, characterize hemorrhage location and extent (including intraventricular extension), and to support treatment decision-making (surgical evacuation vs conservative management). The decision to proceed with surgical evacuation was made by the treating neurosurgical team based on clinical status, imaging findings, and institutional practice.

Patients were classified according to the surgical approach used for hematoma evacuation into two groups: endoscopic-assisted procedures and conventional craniotomy. The choice of approach reflected surgeon judgment and case-specific anatomical and clinical considerations.

Endoscopic-assisted hematoma evacuation (neuroendoscopic surgery)

Endoscopic-assisted evacuation was performed using a 30° cranial endoscope (8 mm diameter) with suction as the principal evacuation instrument. Electromagnetic neuronavigation was used when appropriate to determine the entry point and to plan a safe surgical corridor to the hematoma. The procedure was performed under general anesthesia or, in selected stabilized patients, under local anesthesia. In most cases, rigid head fixation with a Mayfield clamp was not required.

Trajectory planning was individualized according to hematoma location. For lobar/subcortical hemorrhages, the entry point was selected to minimize the distance from the calvarial surface to the

hematoma, and the corridor was aligned parallel to the long axis of the hematoma whenever feasible. If cortical transgression was required, the approach was planned to avoid eloquent cortical regions (e.g., primary motor, language, and visual areas). For putaminal hemorrhages, a parafascicular trajectory was preferred, using Kocher's point or a modified frontal entry tailored to hematoma shape and location.

The procedure began with an approximately 3-cm linear skin incision, followed by a burr hole. The dura was coagulated and opened in an X-shaped fashion. A transparent sheath was commonly used as a working channel to reach the hematoma margin and to permit continuous visualization of the corridor, particularly in the event of iatrogenic bleeding.

Hematoma evacuation was performed under endoscopic visualization using suction with continuous/iterative irrigationto facilitate clot mobilization and to maintain a clear operative field. Hemostasis was achieved using endoscopic bipolar coagulation and adjunctive topical hemostatic agents as required. No routine cavity drain or external ventricular drainage was placed as part of the endoscopic-assisted procedure (Fig. 2.).

Conventional craniotomy (with selective decompressive craniectomy)

Conventional craniotomy represents a standard open approach for intracerebral hematoma evacuation. In selected cases with pronounced intraoperative brain swelling, anticipated postoperative edema, or substantial residual hematoma after evacuation, a decompressive craniectomy was performed instead of replacing the bone flap. The decision to replace the bone flap (craniotomy) versus leave it off with duraplasty (craniectomy) was made intraoperatively by the attending neurosurgeon based on brain relaxation and the perceived extent of evacuation. When a decompressive strategy was selected, duroplasty was typically performed.

The operative goal was maximal safe clot removal, aiming to minimize residual hematoma volume. In this workflow, near-complete evacuation (often operationally referred to as "gross-total" evacuation) corresponded to a small residual cavity component (typically ≤ 5 mL), whereas residual volumes up to 20 mL were considered clinically acceptable and did not routinely mandate early revision, provided the patient remained neurologically stable.

Microsurgical visualization was used to facilitate clot removal and hemostasis, improving operative field illumination and enabling precise bipolar coagulation. Surgical corridors were selected according to hematoma location. Lobar hematomas were approached via a tailored craniotomy centered over the hemorrhage, most commonly using frontal, parietal, or occipital trajectories depending on lesion topography. For putaminal hematomas, a pterional craniotomy with Sylvian fissure dissection was the predominant approach, followed by evacuation of the hematoma through the planned corridor (Fig. 3).

Calculation of hematoma volume

All patients underwent non-contrast brain CT preoperatively and at least twice postoperatively according to the institutional protocol (first scan within 6 hours after surgery and a second scan at 24 hours). CT image datasets were exported in DICOM format and analyzed using 3D Slicer (open-source medical image computing platform)(6).

Hematoma segmentation was performed on non-contrast CT using threshold-based voxel selection with an attenuation range of 50–100 Hounsfield units (HU) to identify the hyperdense hemorrhagic component on each axial slice. A three-dimensional label map was generated from the slice-wise segmentation, and hematoma volume (mL) was computed from the cumulative voxel volume. This volumetric approach is less operator-dependent than the ABC/2 approximation and is particularly suitable for irregularly shaped hematomas(7, 8).

Residual hematoma volume was defined as the hematoma volume measured on the early postoperative CT (≤ 6 h). Hematoma evacuation effectiveness (HEE, %) was calculated as:

$$\mathrm{HEE} = \frac{V_{\mathrm{preop}} - V_{\mathrm{postop}}}{V_{\mathrm{preop}}} \times 100\%$$

where V_{preop} is the preoperative hematoma volume and V_{postop} is the residual hematoma volume on the early postoperative CT.

Postoperative management

After hematoma evacuation, all patients were admitted to the neurosurgical intensive care unit (NICU) for standardized postoperative monitoring and management. Systolic blood pressure was actively controlled with a target < 160 mmHg, using intravenous antihypertensive therapy as required, while avoiding clinically significant hypotension(9, 10). Blood pressure was monitored using intermittent non-invasive cuff measurements or continuous invasive arterial line monitoring, according to clinical indication and hemodynamic stability. Intravenous fluid therapy was carefully titrated to maintain euvolemia and to avoid excessive fluid administration.

All patients received standard postoperative care according to institutional practice, including symptomatic/supportive treatment and early mobilization with rehabilitation therapy. Where available and clinically indicated, early hyperbaric oxygen therapy was administered as part of postoperative supportive care.

Outcome: early postoperative rebleeding

Routine postoperative CT imaging was performed within 6 hours and again at 24 hours after surgery. Early postoperative rebleeding was assessed within 24 hours and defined radiologically as new or increased hyperdensitycompatible with hemorrhage within the hematoma cavity and/or the pericavitary

surrounding brain on follow-up CT relative to the early postoperative CT, irrespective of the amount of residual hematoma after the index evacuation.

To minimize misclassification of residual hematoma as rebleeding, the early postoperative CT served as the radiological baseline for residual blood, and operative reports were reviewed to corroborate the anatomical location of the evacuation cavity. All postoperative CT scans were independently reviewed by two neurosurgeons blinded to each other's assessment; disagreements were resolved by consensus, with adjudication by a senior neurosurgeon when required.

Results

A total of 111 patients were included, with 76 (68.5%) treated by conventional craniotomy and 35 (31.5%) treated by endoscopic-assisted procedures. The two groups were broadly comparable with respect to baseline characteristics. Mean age did not differ significantly between groups (64.97 years [range 33–78] vs 63.28 years [range 35–79]; p = 0.124), and sex distribution was similar (craniotomy 35/41 M/F vs endoscopic-assisted 19/16 M/F). Preoperative hematoma burden was comparable, with no significant difference in mean hematoma volume (56.3 mL [range 28–100] vs 52.1 mL [range 37–99]; p = 0.187).

Postoperative radiological endpoints favored the endoscopic-assisted approach. Residual hematoma volume on early postoperative CT was significantly lower in the endoscopic-assisted group (3.9 mL [range < 1–25]) compared with craniotomy (10.1 mL [range < 1–46]; p < 0.001). Consistently, hematoma evacuation effectiveness (HEE) was higher with endoscopic-assisted procedures (92.5% [range 76–99]) than with craniotomy (82.1% [range 55–99]; p < 0.001) (Table 1).

Table 1
Comparison of Hematoma Evacuation Effectiveness Between the Two Groups

Parameter	Conventional Craniotomy (N = 76)	Endoscopic-Assisted Procedures (N = 35)	p-value
Age, years	64.97 (range: 33–78) *	63.28 (range: 35–79) *	0.124
Sex, M/F	35/41	19/16	
Mean hematoma volume (ml)	56.3 (range: 28–100) *	52.1 (range: 37–99) *	0.187
Residual hematoma volume (ml)	10.1 (range: <1–46)*	3.9 (range: <1–25) *	< 0.001
Hematoma evacuation effectiveness – HEE (%)	82.1 (range: 55–99) *	92.5 (range: 76–99) *	< 0.001
Rebleeding	7 patients	4 patients	0.739
**Range = minimum to maximum*			

Overall, 11/111 (9.9%) patients experienced early postoperative rebleeding. Rebleeding occurred in 7/76 (9.2%) patients in the conventional craniotomy group and 4/35 (11.4%) patients in the endoscopic-

assisted group. The difference between approaches was not statistically significant (two-sided Fisher's exact test, p = 0.739). The corresponding odds ratio for rebleeding was OR = 1.27 for endoscopic-assisted versus craniotomy (exact 95% CI 0.35–4.66) (Table 2).

Table 2
Early postoperative rebleeding by surgical approach (≤ 24 h)

Surgical approach	N	Rebleeding, N (%)	95% CI (Wilson), %	No rebleeding, N (%)
Conventional craniotomy	76	7 (9.2)	4.5–17.8	69 (90.8)
Endoscopic-assisted procedures	35	4 (11.4)	4.5–26.0	31 (88.6)
Overall	**111**	**11 (9.9)**	**5.6–16.9**	**100 (90.1)**

Footnotes Rebleeding assessed within 24 hours postoperatively. 95% confidence intervals (CIs) for proportions were calculated using the **Wilson method.** Between-group comparison: **two-sided Fisher's exact test, p = 0.739.** Effect estimate: **odds ratio (OR) = 1.27** for endoscopic-assisted vs conventional craniotomy (exact 95% CI **0.35–4.66**).

Comorbidity burden was categorized as 0–1 comorbidity versus multimorbidity (≥ 2 chronic conditions). Using this prespecified definition, 78/111 (70.3%) patients were classified as having 0–1 comorbidity and 33/111 (29.7%) as multimorbid.

A marked gradient in early postoperative rebleeding was observed across comorbidity burden strata. Rebleeding occurred in 2/78 (2.6%) patients with 0–1 comorbidity compared with 9/33 (27.3%) patients with multimorbidity. This association was statistically significant (two-sided Fisher's exact test, p = 0.00026) and corresponded to an odds ratio of OR = 14.25 for multimorbidity versus low burden (exact 95% CI 2.879–70.54). The relative risk was RR ≈ 10.64 (27.3% vs 2.6%) (Table 3. and Fig. 4.).

Table 3
Association between comorbidity burden and early postoperative rebleeding (≤ 24 h) (N = 111)

Comorbidity burden	Rebleeding, n/N (%)	No rebleeding, n/N (%)	Odds ratio (OR), exact 95% CI	Fisher's exact p (two-sided)
0–1 comorbidity	2/78 (2.6)	76/78 (97.4)	Reference	—
Multimorbidity (≥ 2 comorbidities)	9/33 (27.3)	24/33 (72.7)	14.25 (2.879–70.54)	0.00026

Footnotes Early postoperative rebleeding was assessed within 24 hours after surgery. Percentages are row-based.

In exploratory analyses evaluating early postoperative physiology and coagulation status, SBP and DBP within the first 24 hours did not differ materially between patients with and without rebleeding (SBP: 136 [124.5–146.0] vs 139 [131.0–148.0] mmHg, p = 0.493; DBP: 89 [81.5–94.5] vs 89 [84.8–94.3] mmHg, p = 0.756). Similarly, aPTT and platelet count showed no clear separation (aPTT: 32.8 [29.4–37.6] vs 31.1

[26.8–34.2] s, p = 0.374; platelets: 209.0 [188.5–229.5] vs 200.5 [166.0–236.5] ×10⁹/L, p = 0.668). By contrast, INR was higher among patients who developed early rebleeding (1.25 [1.13–1.36] vs 1.10 [0.99–1.20], p = 0.008). However, given the limited number of events, these findings were considered hypothesis-generating. In Firth penalized multivariable models including comorbidity burden, anticoagulation exposure, surgical approach, and hematoma volume, the association between INR and rebleeding was attenuated (adjusted OR per 0.1 INR increase 1.10, 95% CI 0.92–1.31), suggesting potential confounding by baseline risk profile and anticoagulant use (Fig. 5).

Discussion

Multimorbidity likely captures converging biological pathways that increase vulnerability to early postoperative bleeding after intracerebral hematoma evacuation. In our cohort, the risk of early postoperative rebleeding was markedly higher in patients with ≥ 2 chronic conditions compared with those with 0–1 comorbidity, underscoring comorbidity burden as a pragmatic marker of systemic fragility. Mechanistically, this association is biologically plausible: hypertension and diabetes promote microangiopathy and impaired vascular integrity; metabolic disease and malnutrition may reduce tissue repair capacity; and chronic liver or renal disease can compromise hemostasis through coagulopathy or platelet dysfunction. Chronic alcohol use may further amplify bleeding propensity via platelet dysfunction, liver impairment, and autonomic instability during withdrawal, which can precipitate perioperative blood pressure surges. Anticoagulant exposure compounds these vulnerabilities by directly impairing clot formation and stability within the surgical cavity.

Hypertension is a key risk factor for ICH and a plausible driver of postoperative rebleeding. Blood pressure surges in the immediate postoperative period may disrupt fragile perforators, destabilize tenuous hemostasis within the evacuation cavity, or precipitate renewed bleeding from diseased small vessels. Therefore, strict blood pressure monitoring and achievement of an appropriate mean arterial pressure target are practical priorities. Earlier neurosurgical practice emphasized careful documentation and control of hypertension while avoiding clinically significant hypotension(10).

Diabetes mellitus contributes via impaired tissue repair, endothelial dysfunction, and small-vessel disease, and may increase infection risk—factors that can adversely affect postoperative stability. In combination with hypertension, diabetes accelerates microangiopathy and atherosclerotic burden, potentially increasing susceptibility to early bleeding. Maintaining normoglycemia and normothermia remains clinically rational in this context.

Cardiovascular disease and obesity frequently cluster with blood pressure instability, antithrombotic exposure, and reduced physiological reserve. Rather than acting as isolated risk factors, these conditions may amplify perioperative vulnerability through intertwined hemodynamic, inflammatory, and metabolic pathways.

Chronic alcohol use is a clinically relevant modifier of bleeding risk through several mechanisms, including thrombocytopenia and platelet dysfunction, malnutrition and immune compromise, and

alcohol-related liver disease with reduced synthesis of coagulation factors. Importantly, abrupt cessation in the perioperative period can trigger withdrawal-related sympathetic activation with blood pressure elevation, which may further increase the likelihood of early rebleeding. Accordingly, a documented alcohol history should prompt targeted laboratory screening and proactive withdrawal prevention strategies(11).

Liver disease is mechanistically linked to postoperative bleeding through reduced synthesis of clotting factors and frequent thrombocytopenia. Moreover, patients with chronic liver disease often exhibit a fragile “rebalanced” hemostatic state that can decompensate under surgical stress. In practice, hepatopathy should prompt expanded hemostasis evaluation and individualized correction strategies, particularly in the early postoperative window(12, 13).

Chronic kidney disease—especially dialysis dependence—is associated with uremic platelet dysfunction, anemia, and blood pressure lability related to fluid shifts. Dialysis sessions may also require anticoagulation, further complicating postoperative management. These factors jointly increase hemorrhagic vulnerability and necessitate careful coordination of dialysis timing, fluid strategy, and anticoagulation approach around surgery (14, 15).

Anticoagulant agents (e.g., warfarin and direct oral anticoagulants) can significantly impair perioperative hemostasis and increase the likelihood of postoperative rebleeding. Patients receiving anticoagulation require structured management, including rapid identification of the agent, appropriate laboratory assessment where applicable, protocolized reversal when indicated, and individualized decisions regarding restart timing. Even when reversal is achieved, baseline anticoagulation exposure may reflect a higher-risk clinical phenotype (e.g., atrial fibrillation, cardiovascular disease), reinforcing the concept that systemic risk profile—and not a single diagnosis—may drive vulnerability to early bleeding (16).

In exploratory analyses, early postoperative SBP and DBP did not differ materially between rebleeding and non-rebleeding cases, suggesting that within the range achieved under institutional blood pressure targets, early blood pressure values alone may not discriminate rebleeding risk. By contrast, INR tended to be higher among patients who developed early rebleeding, consistent with the clinical relevance of coagulation status in the immediate postoperative period. However, this signal was attenuated in penalized multivariable models incorporating comorbidity burden and anticoagulation exposure, indicating potential confounding and supporting interpretation as hypothesis-generating.

Taken together, these findings suggest that comorbidity burden is a pragmatic bedside marker that can support risk stratification and targeted mitigation strategies. In high-burden patients, practical priorities include structured blood pressure management, metabolic stabilization, careful assessment and correction of coagulopathy, proactive alcohol-withdrawal prevention where relevant, and individualized perioperative antithrombotic protocols. Future work in larger cohorts should evaluate whether comorbidity burden can be integrated into decision support to reduce early postoperative rebleeding without compromising other perioperative outcomes.

Limitations

This study has several limitations inherent to its retrospective, observational design. First, residual confounding is likely despite prespecified exposure and outcome definitions. Factors that may influence early postoperative rebleeding include hematoma volume and location (lobar vs deep), intraventricular extension, baseline neurological status, time-to-surgery, perioperative antithrombotic reversal strategy, intraoperative hemostasis quality, and postoperative blood pressure variability. Because treatment decisions and perioperative management were made within routine clinical workflows, these determinants may not be fully captured or standardized in the available records.

Second, the number of early rebleeding events was limited (11/111), restricting statistical power and the complexity of multivariable modeling. Consequently, effect estimates—particularly adjusted odds ratios—are expected to be imprecise, with wide confidence intervals, and should be interpreted as hypothesis-generating rather than definitive. The small event count also increases sensitivity to model specification, collinearity among comorbidities (e.g., cardiovascular disease, atrial fibrillation, and anticoagulation exposure), and the influence of individual outliers.

Third, outcome ascertainment relied on radiological assessment of new or increased hyperdensity on follow-up CT within 24 hours. Although early postoperative CT (≤ 6 h) served as a baseline to mitigate misclassification of residual hematoma as rebleeding, some degree of measurement variability remains possible (e.g., differences in slice thickness, segmentation thresholds, partial volume effects, or subtle interval changes at the cavity margin). In addition, postoperative hyperdensity can occasionally reflect hemostatic material or evolving clot morphology. While operative reports and neurosurgeon review were used to support classification, the outcome remains susceptible to observer-dependent interpretation.

Fourth, the choice of surgical approach (endoscopic-assisted vs conventional craniotomy) was not randomized and reflects surgeon judgment and case-specific anatomical and clinical considerations. Therefore, comparisons between techniques are vulnerable to selection bias and confounding by indication. Moreover, technique-related factors—such as corridor selection, extent of evacuation, hemostatic strategy, and decisions regarding decompressive craniectomy—may influence both residual hematoma and early bleeding risk and should be explored in larger cohorts with more events and formal adjustment strategies.

Fifth, to emphasize the systemic risk profile, the primary analysis focused on comorbidity burden across the combined cohort. While this approach is clinically pragmatic for risk stratification, it may obscure approach-specific interactions (e.g., whether multimorbidity modifies rebleeding risk differently in endoscopic versus open surgery). Future work should evaluate effect modification and include stratified and interaction analyses where event counts permit.

Finally, this was a single-center experience from a tertiary neurosurgical unit, which may limit external validity. Institutional protocols (e.g., postoperative imaging timing, BP targets, ICU management, thresholds for reversal/antithrombotic restart) and local surgical practice patterns may differ across

centers. Prospective multicenter studies with standardized perioperative management and predefined outcome adjudication are warranted to validate these findings and to clarify whether comorbidity burden can be integrated into practical decision support to reduce early postoperative rebleeding.

Declarations

Ethics approval and consent to participate:

The study protocol was reviewed and approved by the Ethics Committee of Univerzitná nemocnica L. Pasteura Košice (Etická komisia Univerzitnej nemocnice L. Pasteura Košice, Rastislavova 43, 041 90 Košice; English: Ethics Committee of University Hospital L. Pasteur Košice), approval No.: 2023/EK/11070, dated 13 November 2023. The study was conducted in accordance with the Declaration of Helsinki and institutional regulations; all data were processed and analyzed in anonymized form. Given the retrospective design, informed consent was obtained when feasible; when not feasible, anonymized data were included in accordance with the ethics approval and institutional regulations.

Funding:

This research received no external funding.

Competing interests:

The authors declare no competing interests.

Clinical trial number:

not applicable.

References

1. Greenberg SM, Ziai WC, Cordonnier C et al (2022) 2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage: A Guideline From the American Heart Association/American Stroke Association. Stroke 53(7):e282–361
2. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B (2012) Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 380(9836):37–43
3. Prapiadou S, Tack RWP, Kimball TN, Mora S, Choksi D, Duperron M et al (2025) Enhancing Comorbidity Management in Patients With Hemorrhagic Stroke via an Electronic Health Record–Linked Best Practice Alert: A Pre/Post Study. J Am Heart Association 14(24):e042302
4. Wafa HA, Marshall I, Wolfe CDA, Xie W, Johnson CO, Veltkamp R et al (2024) Burden of intracerebral haemorrhage in Europe: forecasting incidence and mortality between 2019 and 2050. Lancet Reg Health - Europe 38:100842

5. Skou ST, Mair FS, Fortin M, Guthrie B, Nunes BP, Miranda JJ et al (2022 July) Multimorbidity Nat Rev Dis Primers 14(1):48
6. Fedorov A, Beichel R, Kalpathy-Cramer J et al (2012) 3D Slicer as an image computing platform for the Quantitative Imaging Network. Magn Reson Imaging 30(9):1323–1341
7. Dowlatshahi D, Brouwers HB, Demchuk AM, Hill MD, Aviv RI, Ufholz LA et al (2016) Predicting Intracerebral Hemorrhage Growth With the Spot Sign: The Effect of Onset-to-Scan Time. Stroke 47(3):695–700
8. Xu X, Chen X, Zhang J, Zheng Y, Sun G, Yu X et al (2014) Comparison of the Tada Formula With Software Slicer: Precise and Low-Cost Method for Volume Assessment of Intracerebral Hematoma. Stroke 45(11):3433–3435
9. Basali A, Mascha EJ, Kalfas I, Schubert A (2000) Relation between Perioperative Hypertension and Intracranial Hemorrhage after Craniotomy. Anesthesiology. July 1;93(1):48–54
10. Qureshi AI, Palesch YY, Barsan WG et al (2016) Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage. N Engl J Med 375(11):1033–1043
11. The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management (2020) J Addict Med 14(3S):1–72
12. Lisman T, Porte RJ (2010) Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. Blood 116(6):878–885
13. Lisman T, Hernandez-Gea V, Magnusson M, Roberts L, Stanworth S, Thachil J et al (2021) The concept of rebalanced hemostasis in patients with liver disease: Communication from the ISTH SSC working group on hemostatic management of patients with liver disease. J Thromb Haemost 19(4):1116–1122
14. Mezzano D, Tagle R, Panes O, Pérez M, Downey P, Muñoz B et al (1996) Hemostatic Disorder of Uremia: The Platelet Defect, Main Determinant of the Prolonged Bleeding Time, Is Correlated with Indices of Activation of Coagulation and Fibrinolysis. Thromb Haemost 76(03):312–321
15. Kourtidou C, Tziomalos K (2023) Epidemiology and Risk Factors for Stroke in Chronic Kidney Disease: A Narrative Review. Biomedicines 11(9):2398
16. Hart RG, Diener HC, Yang S, Connolly SJ, Wallentin L, Reilly PA et al (2012 June) Intracranial Hemorrhage in Atrial Fibrillation Patients During Anticoagulation With Warfarin or Dabigatran: The RE-LY Trial. Stroke 43(6):1511–1517

Figures

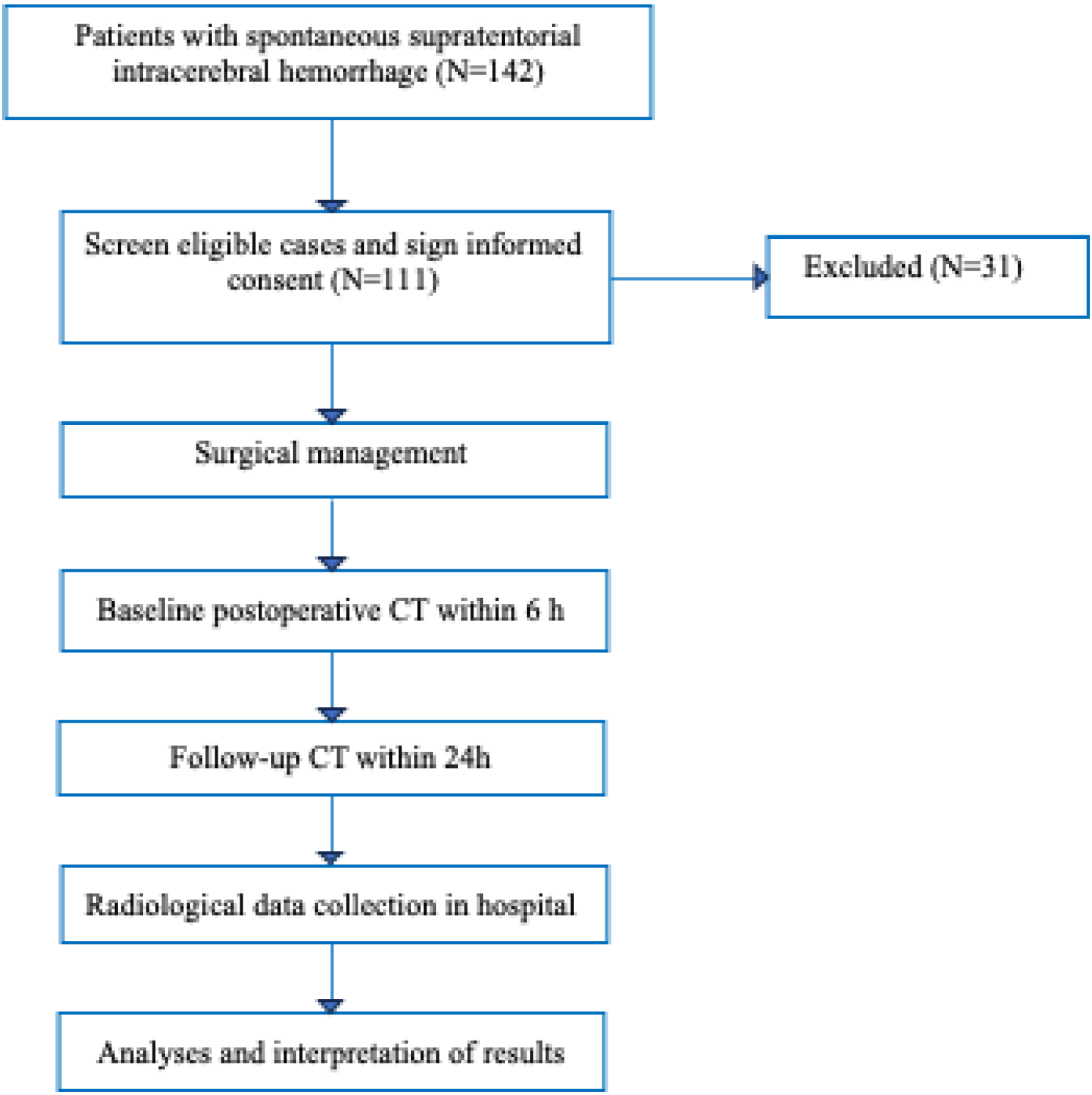


Figure 1

Flowchart of the study design.

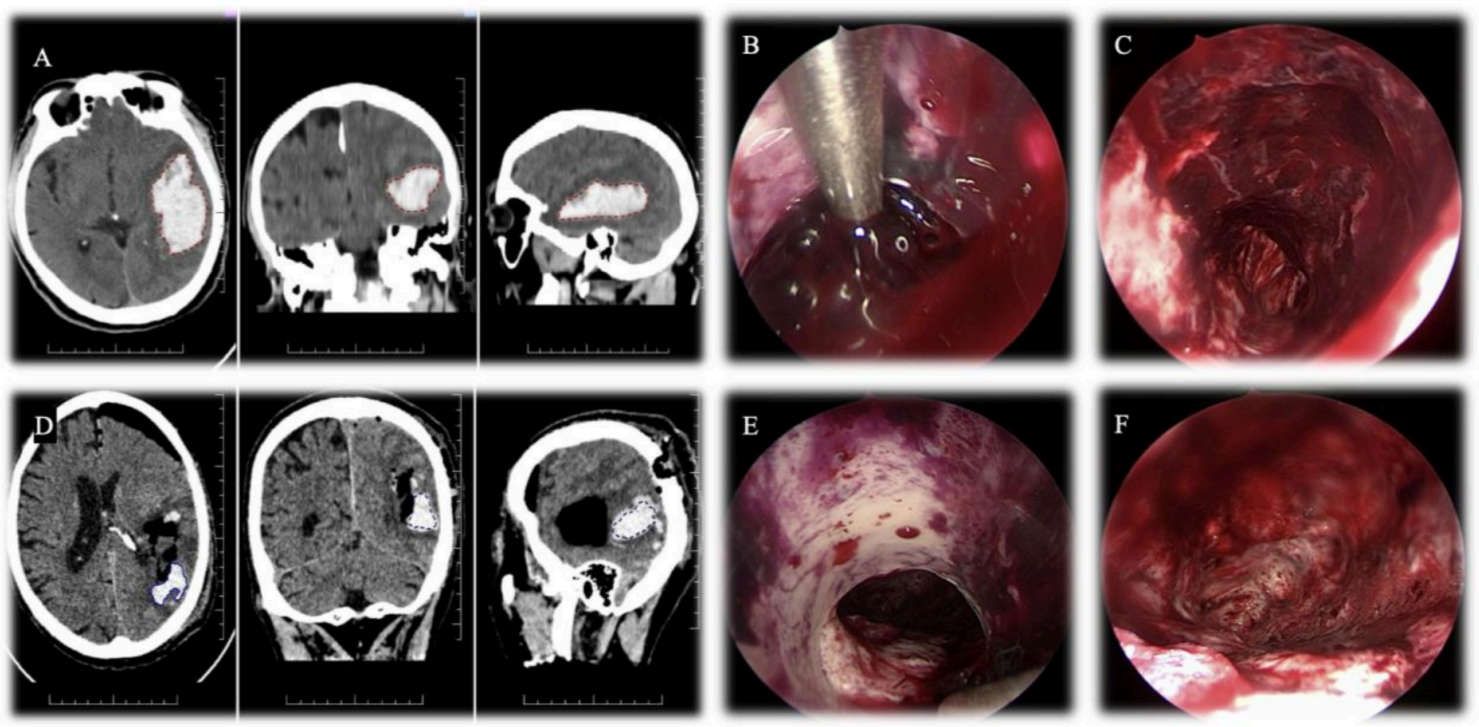


Figure 2

A) CT scan of a lobar hematoma in the temporal lobe in the axial, coronal, and sagittal planes (red

outline). Hematoma volume calculated using dedicated software: 52 mL. B) endoscopic visualization of the

hematoma and endoscope-assisted aspiration. C) the cavity after partial hematoma removal, with visualization of residual clot. D) calculation and visualization of the residual volume (software-based, in three projections) after endoscopic evacuation of the intracerebral hematoma: residual volume 7 mL (blue outline). E) endoscopic view through the working channel and use of a transparent sheath. F) postoperative endoscopic view of the cavity

after hematoma evacuation—no residual hematoma.

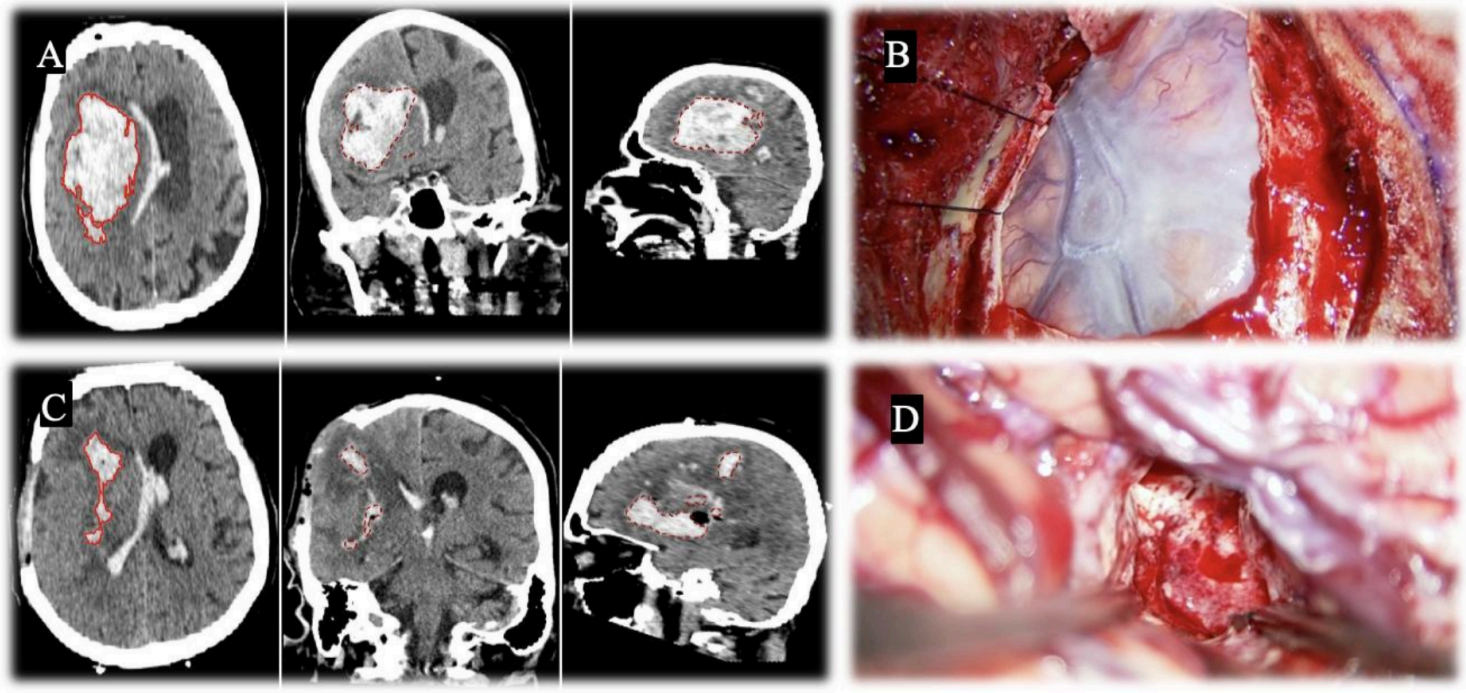


Figure 3

A) CT scan of putaminal hemorrhage. Hematoma volume: 92 mL. B) pterional craniotomy, durotomy, and visualization of the Sylvian fissure prior to dissection and approach to the putaminal hemorrhage. C) Status after evacuation of the putaminal hemorrhage via a conventional craniotomy approach. Residual volume: 15 mL. HEE = 84%. D) microscopic view after microsurgical evacuation of the putaminal hematoma.

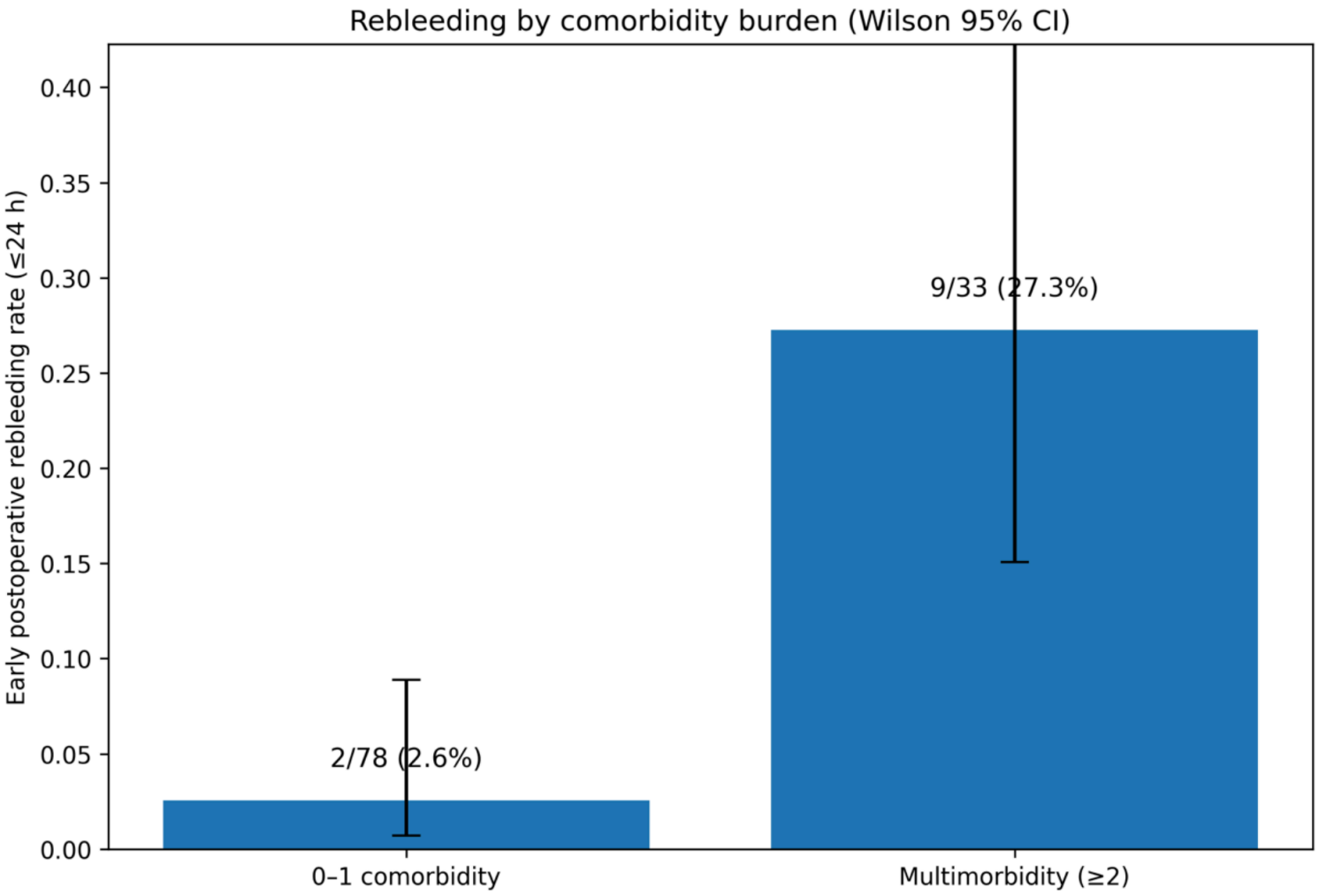


Figure 4

Early postoperative rebleeding by comorbidity burden. Early postoperative rebleeding (≤24 h) occurred in 2/78 (2.6%) patients with 0–1 comorbidity and in 9/33 (27.3%) patients with multimorbidity (≥2 chronic conditions). Bars represent proportions with **Wilson 95% confidence intervals**.

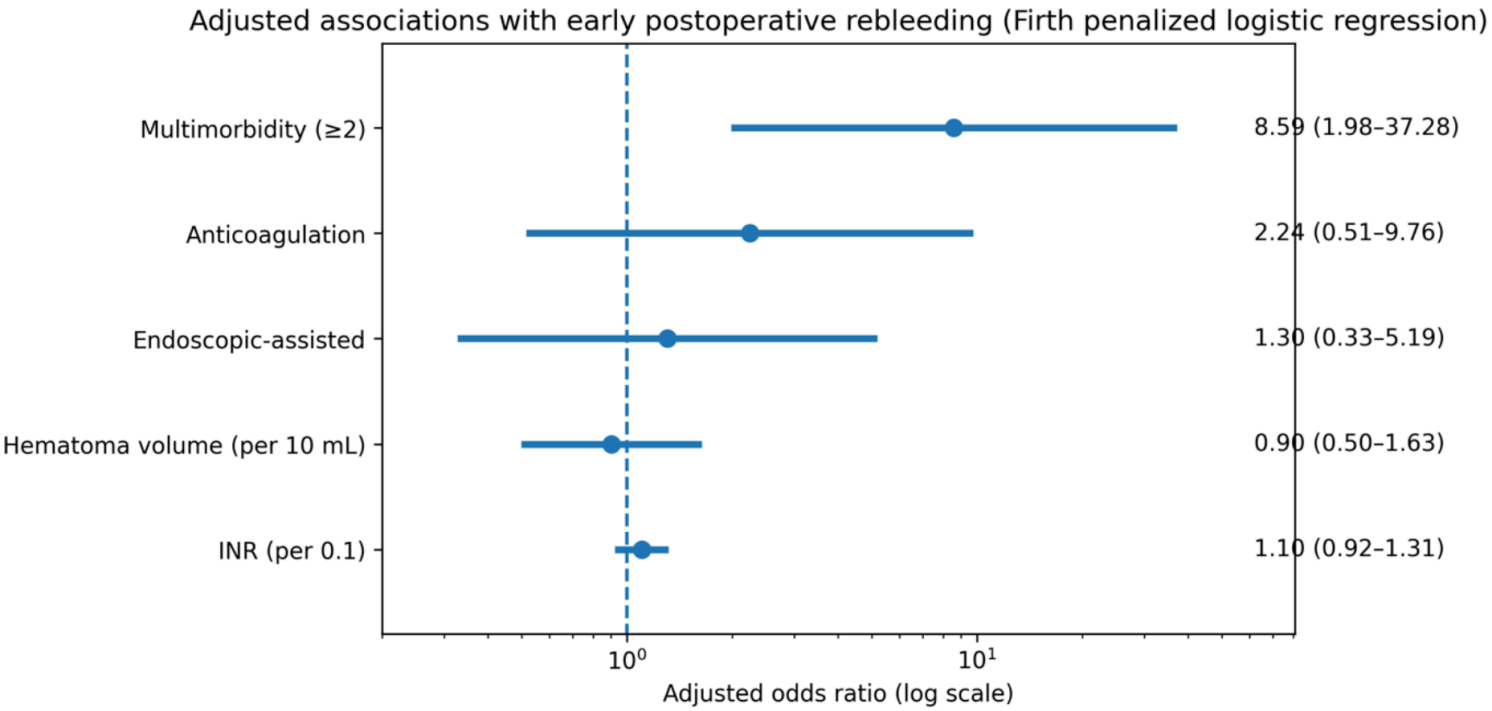


Figure 5

Adjusted associations with early postoperative rebleeding (Firth penalized logistic regression). Forest plot of adjusted odds ratios (ORs) with 95% confidence intervals for clinically relevant covariates, including comorbidity burden, anticoagulation exposure, surgical approach, hematoma volume, and INR (per 0.1 increase). The dashed vertical line indicates OR = 1. Given the limited number of rebleeding events, the model is interpreted as **hypothesis-generating.**